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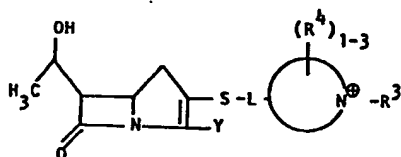
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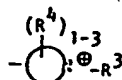
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Carbapenems having an externally alkylated mono- or bicyclic 2-quaternary heteroarylalkylthio substituent.

Carbapenems having the formula:



wherein



is a mono- or bicyclic quaternary heteroaryl, their preparation and antibiotic use are disclosed.

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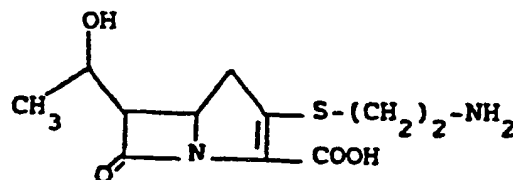
TITLE OF THE INVENTION

CARBAPENEMS HAVING AN EXTERNALLY ALKYLATED MONO- OR BICYCLIC 2-QUATERNARY HETEROCARYLALKYLTHIO SUBSTITUENT

20 BACKGROUND OF THE INVENTION

The present invention is concerned with carbapenems antibiotics having a quaternary mono- or bicyclic heteroaryl containing group in the 2-position.

25 Thienamycin is a known carbapenem, broad spectrum antibiotic of the formula:



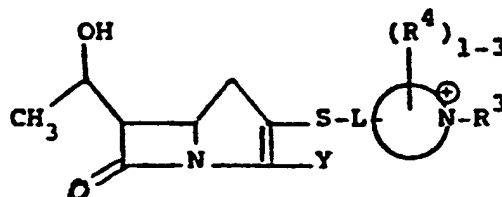
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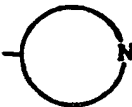
Other derivatives of A are also known.

The present externally alkylated mono- or bicyclic 2-quaternary heteroarylalkylthio substituted carbapenems have an antibiotic spectrum equal to or better than A. The present carbapenems also are more resistant than A to degradation by the dehydropeptidase enzyme DHP-I.

SUMMARY OF THE INVENTION

Carbapenems having the formula:

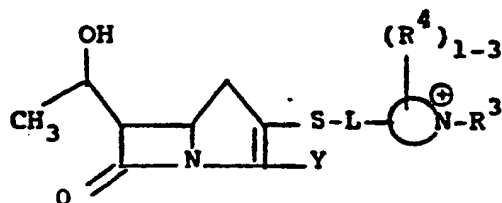


wherein R³ is a quaternizing substituent, R⁴ is a ring hydrogen or substituent, L is a covalent bond or a bridging group,  is mono- or bicyclic heteroaryl, and

Y is a carboxy containing substituent.

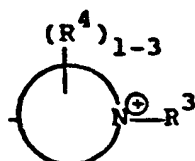
DETAILED DESCRIPTION OF THE INVENTION

The invention is embodied in a compound having the formula:



wherein:

- L is a covalent bond or a bridging group selected from $-(CH_2)_{1-4}S-$; $-(CH_2)_{1-4}O-$; $-(CH_2)_{1-4}X-(CH_2)_{1-4}$ where X=O, S, NH, or $N(C_1-C_6)alkyl$; substituted or unsubstituted C_1-C_4 straight, C_1-C_6 branched or C_3-C_7 cycloalkyl groups wherein the substituents are selected from C_1-C_6 alkyl, $O-C_1-C_6$ alkyl, $S-C_1-C_6$ alkyl, halo, OH, CF_3 , CN, NH_2 , NHC_1-C_6 alkyl, $N(C_1-C_6 alkyl)_2$, CO_2H , $CONH_2$, $CONH(C_1-C_6 alkyl)$, and $CON(C_1-C_6 alkyl)_2$;
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is a mono- or bicyclic heteroarylium group

containing from 5-11 ring atoms of which up to 5 are heteroatoms wherein R^3 is:

- 30
- 1) an unsubstituted or substituted C_1-C_6 alkyl radical;
 - 2) an unsubstituted or substituted C_1-C_6 alkenyl radical;

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- 3) an unsubstituted or substituted
C₁-C₆ alkynyl radical;
- 4) a C₃-C₇ cycloalkyl radical in which
the ring is substituted or
5 unsubstituted and one or more atoms may
be replaced by a heteroatom;
- 5) a C₃-C₇ cycloalkyl methyl radical
in which the ring may be substituted
and one or more atoms may be replaced
10 by a heteroatom;
- 6) an unsubstituted or substituted
C₅-C₇ cycloalkenyl radical;
- 7) an unsubstituted or substituted
bivalent C₂-C₆ alkylidene radical,
15 optionally interrupted by a heteroatom,
and joined to the heteroaryl group
to form a ring which is carbocyclic or
in which one or more atoms is replaced
by a heteroatom. The new ring may
20 contain one or more double bonds;
- 8) an unsubstituted or substituted phenyl
or heteroaryl radical;
- 9) an unsubstituted or substituted phenyl
(C₁-C₄ alkyl) or heteroaryl
25 (C₁-C₄ alkyl) radical;
- 10) a cyano (C₁-C₄ alkyl) radical;
- 11) a carbamoyl (C₁-C₄ alkyl) radical;
30
- 12) a hydroxy (C₁-C₄ alkyl) radical;

13) an amino (C_1-C_4 alkyl) radical in which the nitrogen atom is unsubstituted or substituted with one to three C_1-C_4 alkyl groups;

14) an acidic side-chain of the structure

$-(CH_2)_n-X-(CH_2)_m-Y-A$ where:

$n = 0-4$

$m = 0-4$

$X = CHR^S, CH=CH, \text{phenylene } (-C_6H_4-), NH, N(C1-C4 \text{ alkyl}), O, S, S-O, C-O, SO_2, SO_2NH, CO_2, CONH, OCO, OC-O, NHC=O;$
 $R^S = H, O(C1-C4 \text{ alkyl}), NH, NH(C1-C4 \text{ alkyl}), N(C1-C4 \text{ alkyl}), CN, CONH, CON(C1-C4 \text{ alkyl}), CO_2H, SO_2NH, SO_2NH(C1-C4 \text{ alkyl});$

$Y = \text{single bond}, NH, N(C1-C4 \text{ alkyl}), O, S;$

$A = \text{an acidic function such as carboxy } (CO_2H), \text{ phosphono } [P=O(OH)_2], \text{ alkylphosphono } \{P=O(OH)-[C(C_1-C_4 \text{ alkyl})]\}, \text{ alkylphosphinyl } [P=O(OH)-(C_1-C_4 \text{ alkyl})], \text{ substituted phosphoramido } [P=O(OH)NH(C_1-C_4 \text{ alkyl}) \text{ and } P=O(CH)NHR^X], \text{ sulfinio } (SO_2H), \text{ sulfo } (SO_3H), \text{ 5-tetrazolyl } (CN_4H), \text{ arylsulfonamido } (SO_2NHR^X) \text{ and acylsulfonamides represented by the structures } CONHSO_2(C_1-C_4 \text{ alkyl}), COMHSO_2N(C_1-C_4 \text{ alkyl})_2 - SO_2NHCO(C_1-C_4 \text{ alkyl}) \text{ and } SO_2NHCOR^X;$

$R^X = \text{aryl or heteroaryl as defined above};$

wherein the substituents in the above definitions of R^3 are independently selected from the group consisting of the definitions of R^4 set out below;

R^4 is independently selected from:

- a) a trifluoromethyl group;
- b) a halogen atom;
- c) an unsubstituted or substituted C_1-C_4 alkoxy radical;
- d) a hydroxy group;
- e) an unsubstituted or substituted (C_1-C_6 alkyl) carbonyloxy radical;
- f) a carbamoyloxy radical which is unsubstituted or substituted on nitrogen with one or two C_1-C_4 alkyl groups;
- g) a C_1-C_6 alkylthio radical, C_1-C_6 alkylsulfinyl radical or C_1-C_6 alkylsulfonyl radical, each of which is unsubstituted or substituted on the alkyl group;
- h) a sulfamoyl group which is unsubstituted or substituted on nitrogen by one or two C_1-C_4 alkyl groups;
- i) an amino group;

- j) a mono (C_1-C_4 alkyl) amino or
di(C_1-C_4 alkyl)amino group, each of
which is unsubstituted or substituted
on the alkyl group;
- 5 k) a formylamino group;
- l) an unsubstituted or substituted
(C_1-C_6 alkyl)carbonylamino radical;
- m) a (C_1-C_4 alkoxy) carbonylamino
radical;
- 10 n) a ureido group in which the terminal
nitrogen is unsubstituted or
substituted with one or two C_1-C_4
alkyl groups;
- o) a (C_1-C_6 alkyl)sulfonamido group;
- 15 p) a cyano group;
- q) a formyl or acetalized formyl radical;
- r) an unsubstituted or substituted
(C_1-C_6 alkyl)carbonyl radical
wherein the carbonyl is free or
acetalized;
- 20 s) an unsubstituted or substituted
phenylcarbonyl or heteroarylcarbonyl
radical;
- 25 t) a hydroximinomethyl radical in which
the oxygen or carbon atom is optionally
substituted by a C_1-C_4 alkyl group;
- u) a (C_1-C_6 alkoxy)carbonyl radical;
- 30 v) a carbamoyl radical which is
unsubstituted or substituted on
nitrogen by one or two C_1-C_4 alkyl
groups;

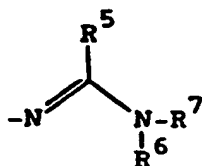
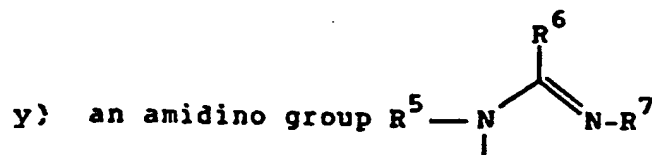
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- w) an N-hydroxycarbamoyl or N(C₁-C₄ alkoxy)carbamoyl radical in which the nitrogen atom may be additionally substituted by a C₁-C₄ alkyl group;
- x) a thiocarbamoyl group;



where R⁵, R⁶ and R⁷ are independently hydrogen, C₁-C₄ alkyl or wherein two of the alkyl groups together form a C₂-C₆ alkylidene radical optionally interrupted by a heteroatom and joined together to form a ring;

- z) a carboxamidino group
$$\begin{array}{c} \text{NR}^5 \\ || \\ \text{C} \\ / \quad \backslash \\ \text{NR}^6 \quad \text{R}^7 \end{array}$$
 where R⁵, R⁶ and R⁷ are as defined above;

- aa) a guanidinyll group where R⁶ in ab) above is NR⁸R⁹ and R⁸ and R⁹ are as defined for R⁵ through R⁷ above.

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ab) hydrogen;

ac) an unsubstituted or substituted

C_1-C_6 alkyl radical;

ad) an unsubstituted or substituted

C_1-C_6 alkenyl radical;

ae) an unsubstituted or substituted

C_1-C_6 alkynyl radical;

af) a C_3-C_7 cycloalkyl radical in which

the ring is substituted or

unsubstituted and one or more atoms may
be replaced by a heteroatom;

ag) a C_3-C_7 cycloalkyl methyl radical

in which the ring may be substituted

and one or more atoms may be replaced
by a heteroatom;

ah) an unsubstituted or substituted

C_5-C_7 cycloalkenyl radical;

ai) an unsubstituted or substituted phenyl

or heteroaryl radical;

aj) an unsubstituted or substituted phenyl

(C_1-C_4 alkyl) or heteroaryl

(C_1-C_4 alkyl) radical; and

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ak) an acidic side-chain of the structure

-A or $-(CH_2)_n-X-(CH_2)_m-Y-A$ where:

$n = 0-4$

$m = 0-4$

$X = CHR^3$, $CH=CH$, phenylene ($-C_6H_4-$), NH , $N(C1-C4 \text{ alkyl})$,
 O , S , $S=O$, $C=O$, SO_2 , SO_2NH , CO_2 , $CONH$, OCO_2 , $OC=O$, $NHC=O$;
 $R^3 = H$, $O(C1-C4 \text{ alkyl})$, NH_2 , $NH(C1-C4 \text{ alkyl})$, $N(C1-C4 \text{ alkyl})_2$,
 CN , $CONH_2$, $CON(C1-C4 \text{ alkyl})_2$, CO_2H , SO_2NH_2 ,
 $SO_2NH(C1-C4 \text{ alkyl})$;

$Y = \text{single bond}$, NH , $N(C1-C4 \text{ alkyl})$, O , S ;

$A =$ an acidic function such as carboxy (CO_2H),
 phosphono [$P=O(OH)_2$], alkylphosphono [$P=O(OH)-$
 $[C(C_1-C_4 \text{ alkyl})]$], alkylphosphinyl [$P=O(OH)-$
 $(C_1-C_4 \text{ alkyl})$], substituted phosphoramido
 $[P=O(OH)NH(C_1-C_4 \text{ alkyl})$ and $P=O(CH)NHR^X]$,
 sulfinio (SO_2H), sulfo (SO_3H), 5-tetrazolyl
 (CN_4H) , arylsulfonamido (SO_2NHR^X) and acylsul-
 fonamides represented by the structures
 $CONHSO_2(C_1-C_4 \text{ alkyl})$, $CONHSO_2N(C_1-C_4 \text{ alkyl})_2$ -
 $SO_2NHCO(C_1-C_4 \text{ alkyl})$ and SO_2NHCOR^X ;

$R^X = \text{aryl or heteroaryl as defined above}$;


- Y is selected from:
- i) COOH or a pharmaceutically acceptable ester or salt thereof.
 - 5 ii) COOR¹ wherein R¹ is a removable carboxy protecting group.
 - iii) COOM wherein M is an alkali metal, or
 - 10 iv) COO[⊖]; provided that when Y is other than iv) a counterion Z[⊖] is provided.

As used herein, the term "heteroatom" means nitrogen, oxygen, or sulfur, independently selected where more than one heteroatom is involved.

Representative L groups are -CH₂-, -CH(CH₃)-, -CH(C₂H₅)-, -(CH₂)₂₋₄-, -CH(CH₃)-CH₂-, CH₂-CH(OCH₃)-, -CH(CH₃)-(CH₂)₂-, -CH(CH₂OH)-CH₂-, 20 -CH(CF₃)-CH₂-, -CH₂-CH₂-S-, -CH₂-CH₂-O-, -(CH₂)₂-S-CH₂-, -(CH₂)₂-O-CH₂-, a single covalent bond, and the like.

A preferred L group is a substituted or unsubstituted C₁-C₆ linear or branched chain alkyl. A more preferred L group is -CH₂-, -CH(CH₃)- or (CH₂)₂-.

Examples of useful R³ groups are -CH₃,

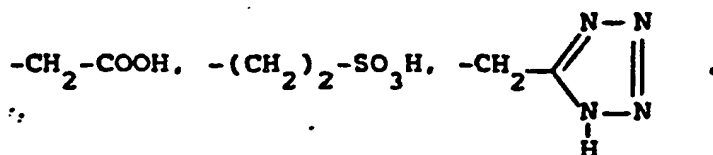
30 -(CH₂)₁₋₃-CH₃, -CH₂--, -(CH₂)₁₋₃-O-CH₃, -CH₂-CN, CH₂-COOC_{1-C3} alkyl, -(CH₂)₂-N(C_{1-C3} alkyl)₂.

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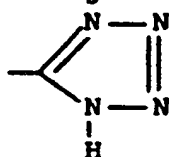
5 -(CH₂)₂-N[⊕](CH₃)₃ and the like.

Preferred R³ groups are the C₁-C₆ alkyls, both substituted and unsubstituted.

Preferred substituents are CN,

CON(CH₃)₂, CONH₂, SOCH₃, SO₂CH₃, CO₂H,

10 SO₃H, SO₂NH₂ and



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Examples of useful R⁴ groups are OH,

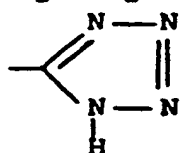
NH₂, N(C₁-C₃alkyl), OC₁-C₄alkyl,

C₁-C₄alkyl, CN, CF₃, CH₂OH and the like.

Preferred R⁴ groups are CO₂H,


CH₂CO₂H, SO₃H, CH₂SO₃H, CONH₂,

20 CH₂CONH₂, CN, CH₂CN, SO₂NH₂



. CH₂P(O)(OCH₃) and the like.

25

The  moiety is mono- or bicyclic

quaternary heteroaryl group having 5-11 ring atoms of which, in addition to the quaternary N[⊕], up to four

30 can be heteroatoms.

Of particular interest and the most preferred group are compounds of the present invention wherein the substituent on the N-containing mono- or bicyclic quaternary heteroaryl group in the 2-position is an acidic function as defined above and the Y substituent in the 3-position is COO^{\ominus} as defined above, thus forming a zwitterion with the positive charge of the quaternary nitrogen.

5 The acidic function is anionic and the compounds are thus anionic zwitterions, i.e., they have a net negative charge. This novel characteristic has been found to result in at least one surprising

10 and important improvement in the biological properties of the compounds reduced CNS side-effects. A more particular group of the compounds, those wherein the acidic function is a sulfoalkyl group of the formula $(\text{C}_{1-4} \text{ alkyl})\text{SO}_3^{\ominus}$, have been found to have

15 the additional surprising and important biological property of enhanced potency against Pseudomonas species, an especially important nosocomial pathogen. In this most preferred group of compounds, it is preferred that the N-containing mono- or

20 bicyclic quaternary heteroaryl group in the 2-position is pyridinium.

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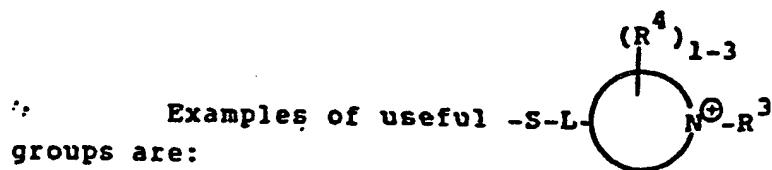
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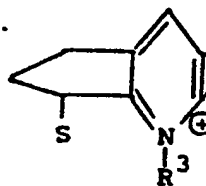
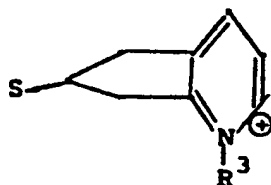
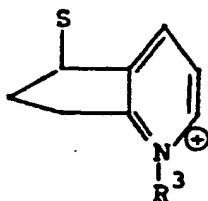
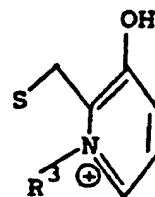
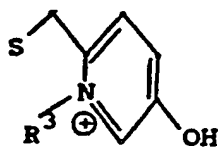
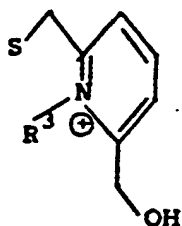
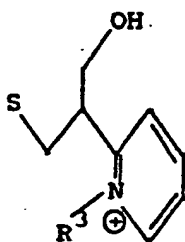
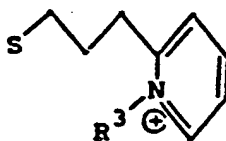
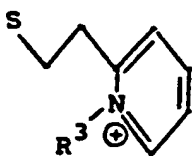
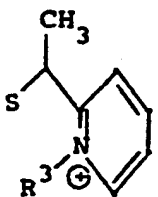
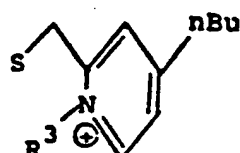
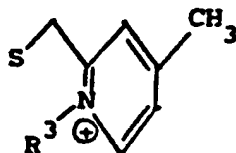
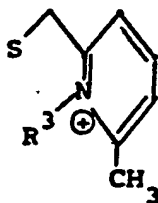
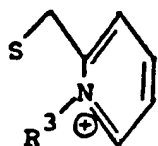
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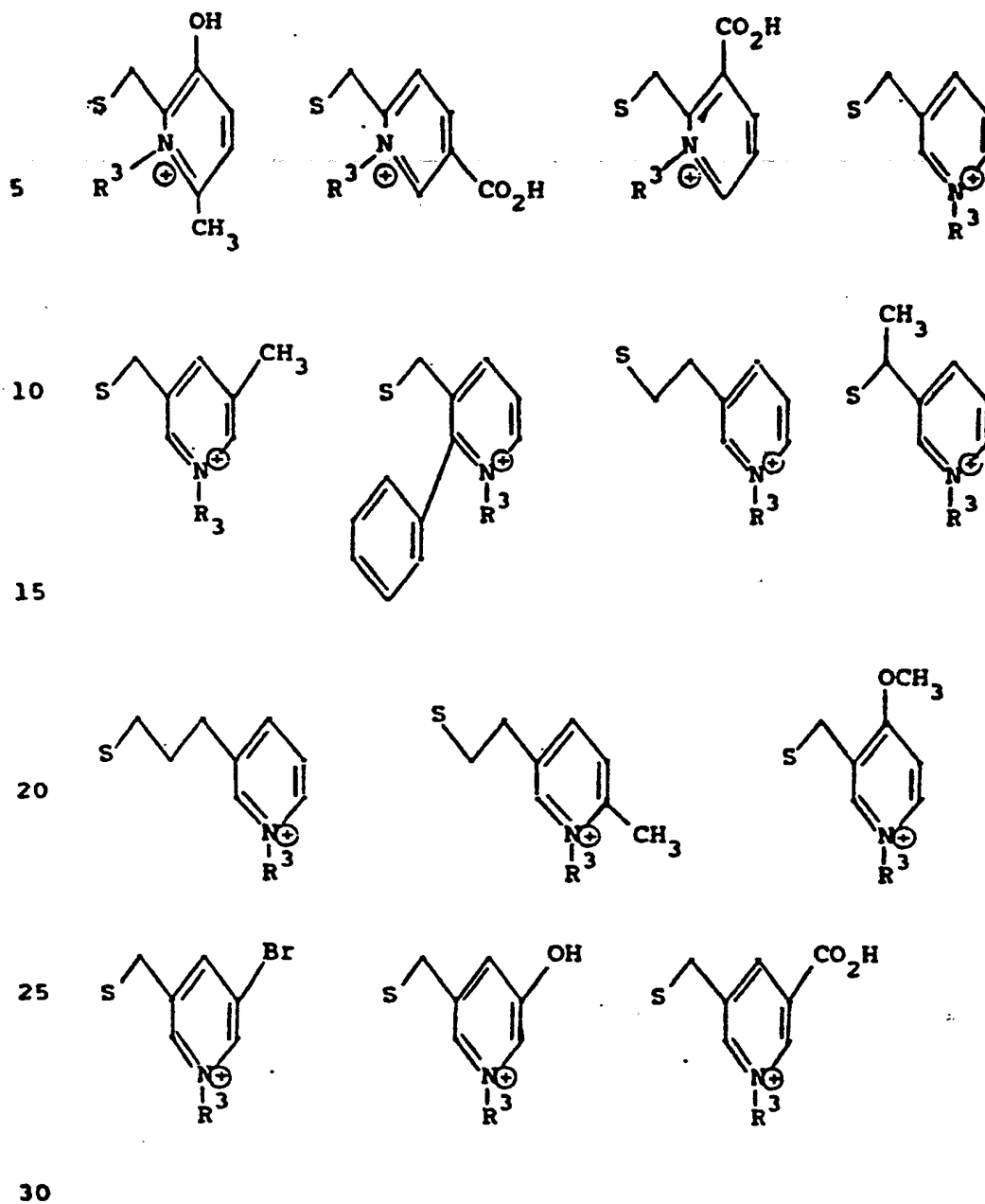
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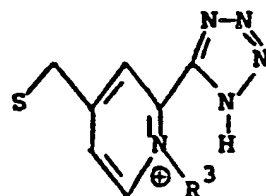
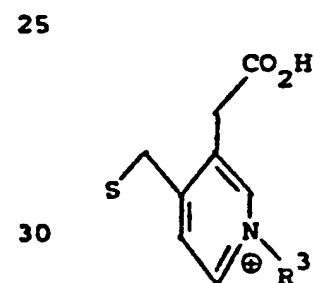
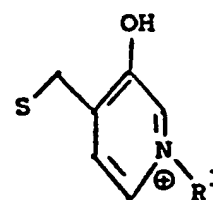
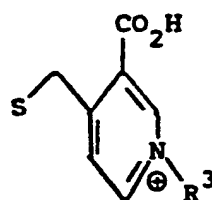
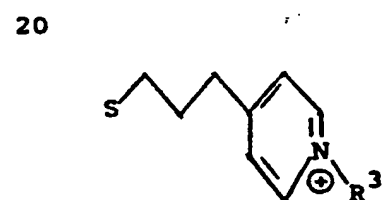
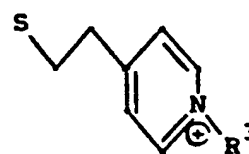
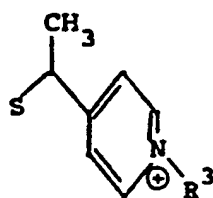
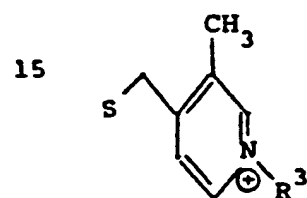
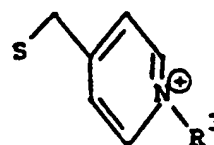
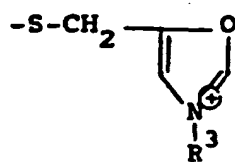
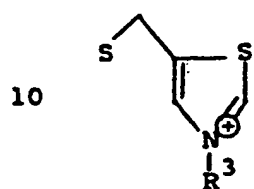
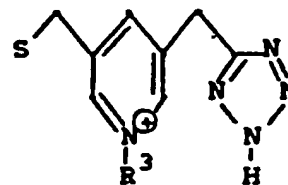
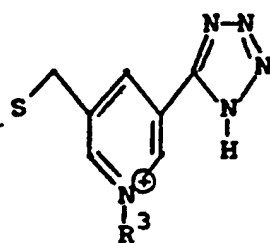
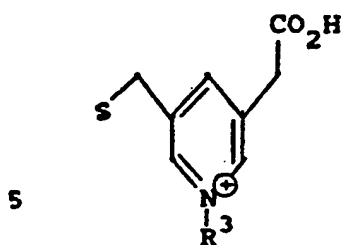
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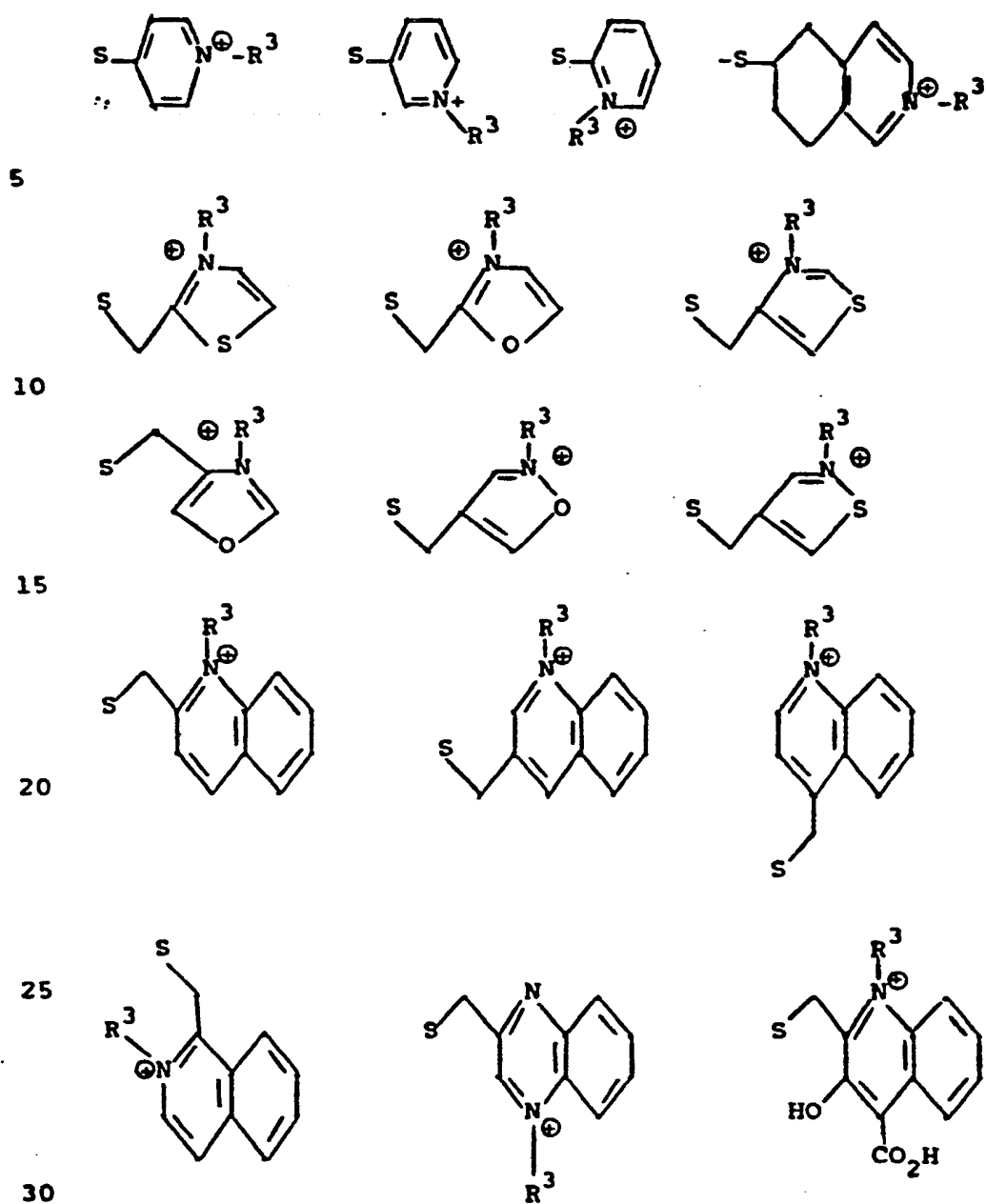


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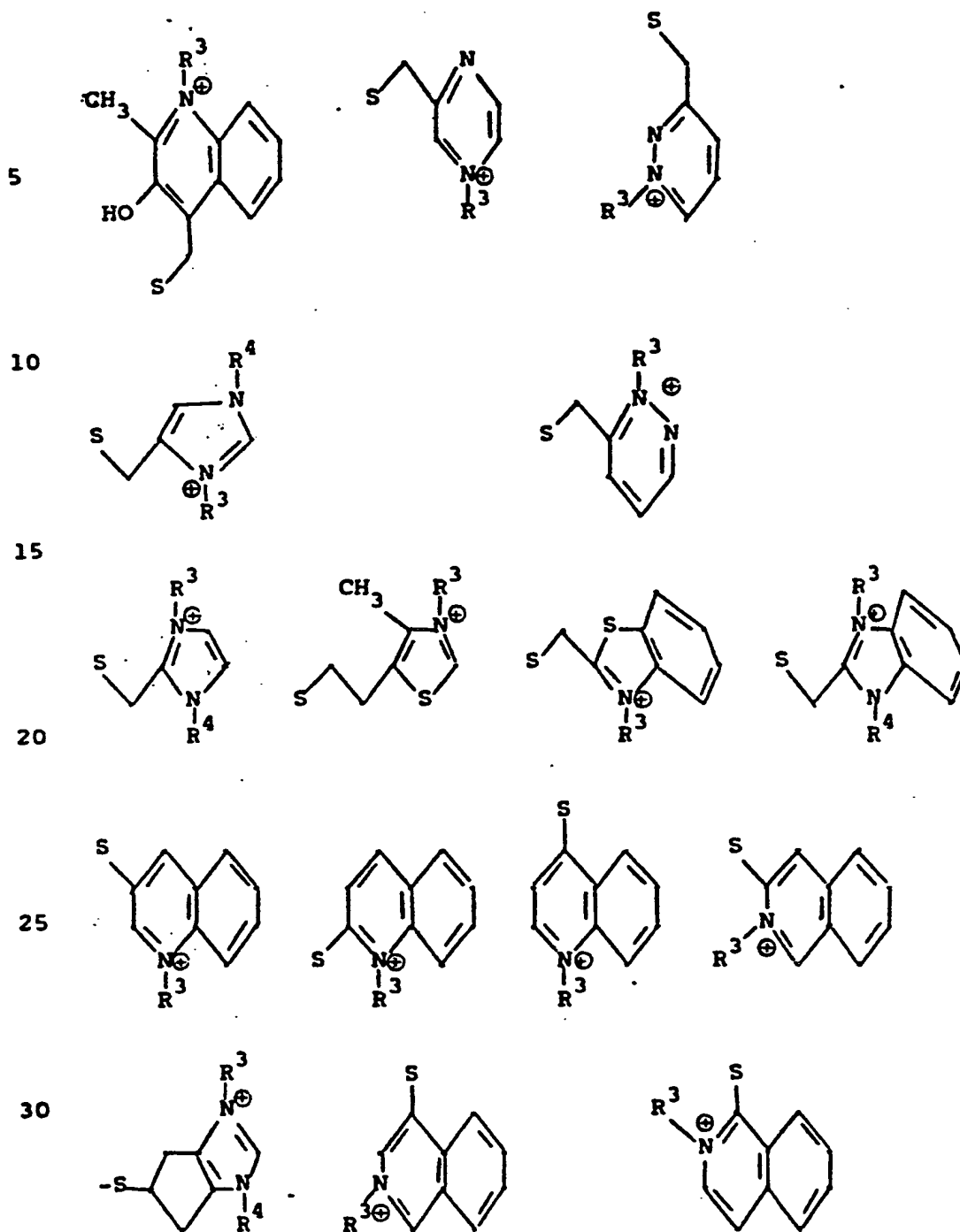


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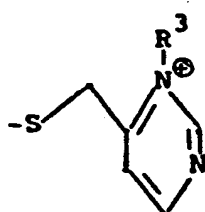
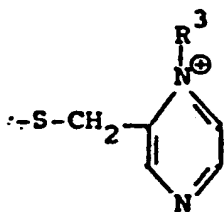
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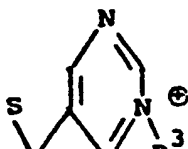
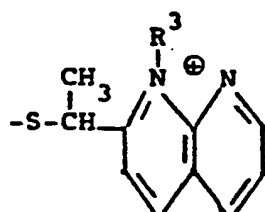
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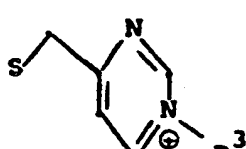
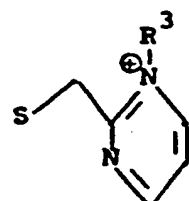
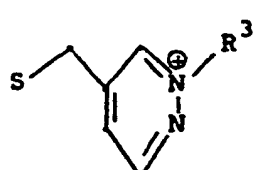
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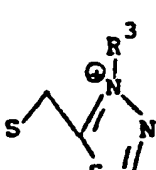
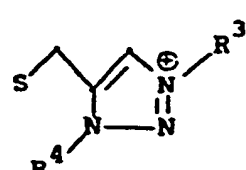
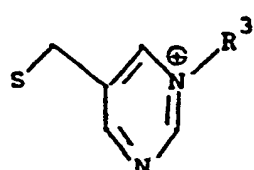
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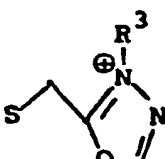
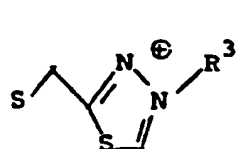
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and the like.


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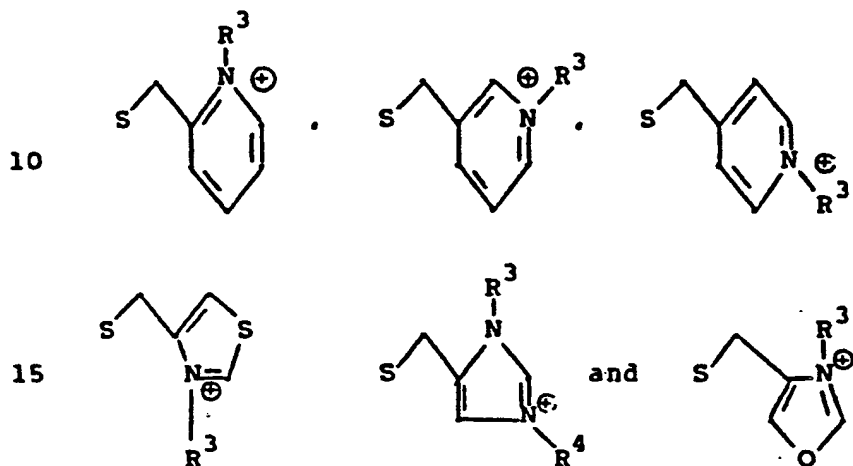
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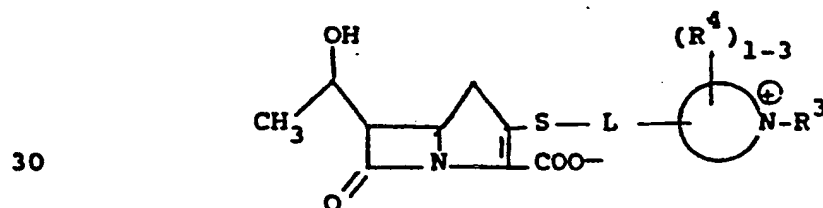
A preferred S-L--R³ group is monocyclic heteroaryl having 5-6 ring atoms and optionally one heteroatom additional to the N atom already present, e.g.,



where R³ and R⁴ are as defined in the preferred list above.

A more preferred subclass includes the nuclei shown above where R³ is CH₃ and R⁴ is CH₃.

The compounds of Formula I include inner (Zwitterion) salts when Y is COO[⊖] e.g.



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or, when Y is other than COO^\ominus , salts with an external, physiologically acceptable counterion z^\ominus such as Cl^\ominus , Br^\ominus , I^\ominus , OCH_3^\ominus , $\text{OSO}_2\text{CF}_3^\ominus$, $\text{OP}(\text{O})(\text{O phenyl})_2^\ominus$ and the like.

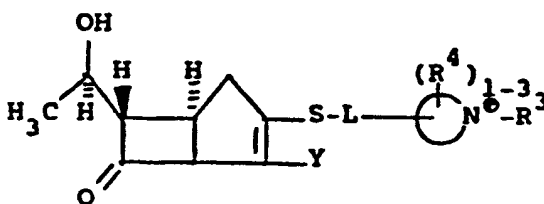
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The inner salts are preferred.

Again, the compounds of Formula I include the stereoisomers as mixtures and as separate isomers.

A preferred isomer configuration is:

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Ia

The compounds of the present invention (I) are valuable antibiotics active against various Gram-positive and Gram-negative bacteria and accordingly find utility in human and veterinary medicine. Representative pathogens which are sensitive to antibiotics I include: Staphylococcus aureus, Escherichia coli, Klebsiella Pneumoniae, Bacillus subtilis, Salmonella typhosa, Pseudomonas and Bacterium proteus. The antibacterials of the invention are not limited to utility as medicaments; they may be used in all manner of industry, for example: additives to animal feed, preservation of food, disinfectants, and in other industrial systems where control of bacterial growth is desired. For example, they may be employed in aqueous compositions in concentrations ranging from 0.1 to 100 parts of

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antibiotic per million parts of solution in order to destroy or inhibit the growth of harmful bacteria on medical and dental equipment and as bactericides in industrial applications, for example in waterbased paints and in the white water of paper mills to inhibit the growth of harmful bacteria.

The compounds of this invention may be used in any of a variety of pharmaceutical preparations. They may be employed in capsule, powder form, in liquid solution, or in suspension. They may be administered by a variety of means; those of principal interest include: topically or parenterally by injection (intravenously or intramuscularly).

Compositions for injection, a preferred route of delivery, may be prepared in unit dosage form in ampules, or in multidose containers. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents. Alternatively, the active ingredient may be in powder form for reconstitution, at the time of delivery, with a suitable vehicle, such as sterile water. Topical applications may be formulated in hydrophobic or hydrophilic bases as ointments, creams, lotions, paints, or powders.

The dosage to be administered depends to a large extent upon the condition and size of the subject being treated as well as the route and frequency of administration -- the parenteral route by injection being preferred for generalized infections. Such matters, however, are left to the routine discretion of the therapist according to

principles of treatment well known in the antibiotic art. In general, a daily dosage consists of from about 5 to about 600 mg of active ingredient per kg of body weight of the subject in one or more treatments per day. A preferred daily dosage for adult humans lies in the range of from about 10 to 240 mg of active ingredient per kg of body weight. Another factor influencing the precise dosage regimen, apart from the nature of the infection and peculiar identity of the individual being treated, is the molecular weight of the chosen species of this invention (I).

The compositions for human delivery per unit dosage, whether liquid or solid, may contain from 0.1% to 99% of active material, the preferred range being from about 10-60%. The composition will generally contain from about 15 mg to about 1500 mg of the active ingredient; however, in general, it is preferable to employ a dosage amount in the range of from about 250 mg to 1000 mg. In parenteral administration, the unit dosage is usually the pure compound I in sterile water solution or in the form of a soluble powder intended for solution.

The preferred method of administration of the formula I antibiotic is parenteral by i.v. infusion, i.v. bolus, or i.m. injection.

For adults, 5-50 mg of Formula I antibiotic per kg of body weight given 2, 3, or 4 times per day is preferred. Preferred dosage is 250 mg to 1000 mg of the Formula I antibiotic given two (b.i.d.) three (t.i.d.) or four (q.i.d.) times per day. More specifically, for mild infections, and particularly

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urinary tract infections, a dose of 250 mg t.i.d. or q.i.d. is recommended. For moderate infections against highly susceptible gram positive and gram negative organisms, a dose of 500 mg t.i.d. or q.i.d. is recommended. For severe, life-threatening infections against organisms at the upper limits of sensitivity to the antibiotic, a dose of 1000 t.i.d. or q.i.d. is recommended.

For children, a dose of 5-25 mg/kg of body weight given 2, 3, or 4 times per day is preferred; a dose of 10 mg/kg t.i.d. or q.i.d. is usually recommended.

Antibiotic compounds of Formula I are of the broad class known as carbapenems or 1-carbade-thiopenems. Certain of these carbapenems are susceptible to attack by a renal enzyme known as dehydropeptidase (DHP). This attack or degradation may reduce the efficacy of the carbapenem antibiotic. Inhibitors of DHP and their use with carbapenem antibiotics are disclosed in the prior art [see published European Patent Applications No. 79102615.6, filed July 24, 1979 (application no. 15573) and No. 82107174.3, filed August 9, 1980 (application no. 72014)].

The present I compounds may, where DHP inhibition is desired or necessary, be combined or used with the appropriate DHP inhibitor as described in the aforesaid published applications. Thus, to the extent that the cited European patent applications 1.) define the procedure for determining DHP susceptibility of the present carbapenems and 2.)

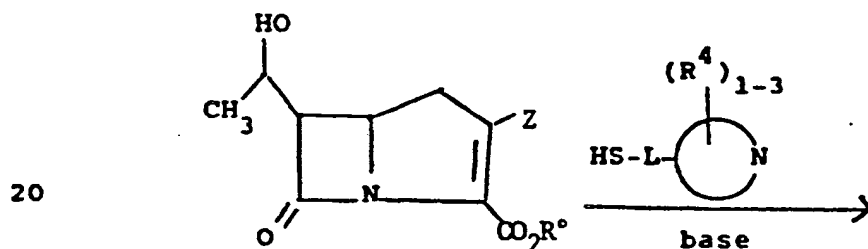
disclose suitable inhibitors, combination compositions and methods of treatment, they are incorporated herein by reference. A preferred weight ratio of I compound:DHP inhibitor in the combination compositions is about 1:1. A preferred DHP inhibitor is 7-(L-2-amino-2-carboxyethylthio)-2-(2,2-dimethylcyclopropanecarboxamide)-2-heptenoic acid or a useful salt thereof.

These combination compositions and their use is another embodiment of the present invention.

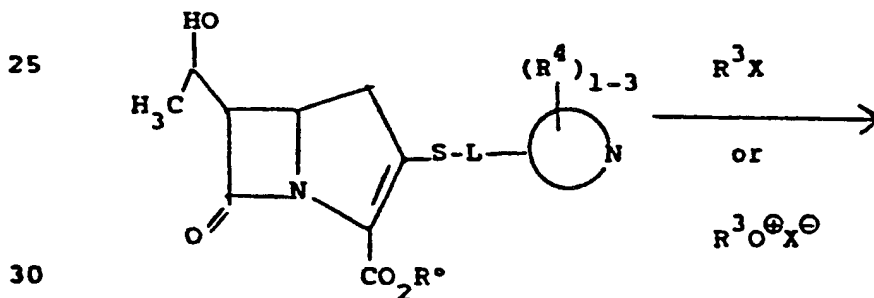
The compounds of Formula I may be prepared by any convenient process.

A. One such process is illustrated in the following reaction equations:

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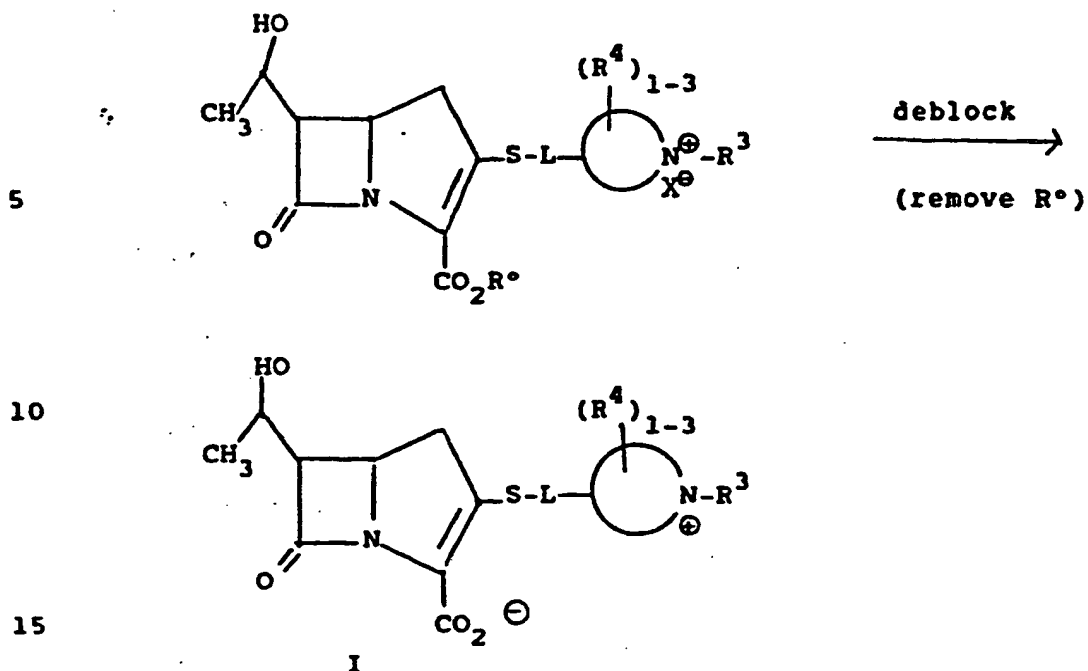


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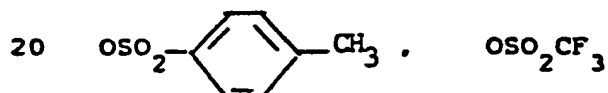
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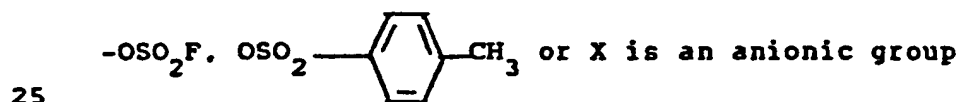
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wherein Z is a leaving group such as $-\text{OPO}(\text{O})_2$.



and the like, X is a leaving group such as Br, I, OSO_2CF_3 ,



such as BF_4 , SbF_5 , PF_6 and the like; and R° is a protecting group such as p-nitrobenzyl or allyl. R^3 , L and R^4 are as defined above.

30 The side chain addition reaction is carried out in a solvent such as acetonitrile, dimethylformamide, dimethylacetamide or N-ethylpyrrolidinone in the presence of a base such as

N,N-diisopropylethylamine, triethylamine or 4-dimethylaminopyridine at a temperature of from -40°C to 25°C for a period of five minutes to ten hours. The alkylation reaction is conducted in a solvent such as dichloromethane, dimethylformamide, acetonitrile or dimethylacetamide at a temperature of from -20°C to 25°C for a period of 1 to 24 hours. The deblocking reaction wherein R^o is p-nitrobenzyl is usually conducted in an aqueous system containing cosolvents such as tetrahydrofuran, ethanol, n-butanol, i-amyl alcohol, or ethyl acetate and a pH 6.8 to 7.0 aqueous buffer. Suitable buffers include phosphate buffers and buffers derived from non-nucleophilic amines such as N-methylmorpholine or morpholinopropane sulfonic acid. The reaction is conducted at 0°C to 40°C for 0.5 to 5 hours under 1-100 atmospheres of hydrogen in the presence of a catalyst such as 10% palladium on carbon or 20% palladium hydroxide on carbon. The final products are purified by ion exchange chromatography and/or reverse phase chromatography. When a pharmaceutically acceptable ester of the final product is desired, the deblocking step is omitted and the appropriate R^o group is incorporated into the starting material.

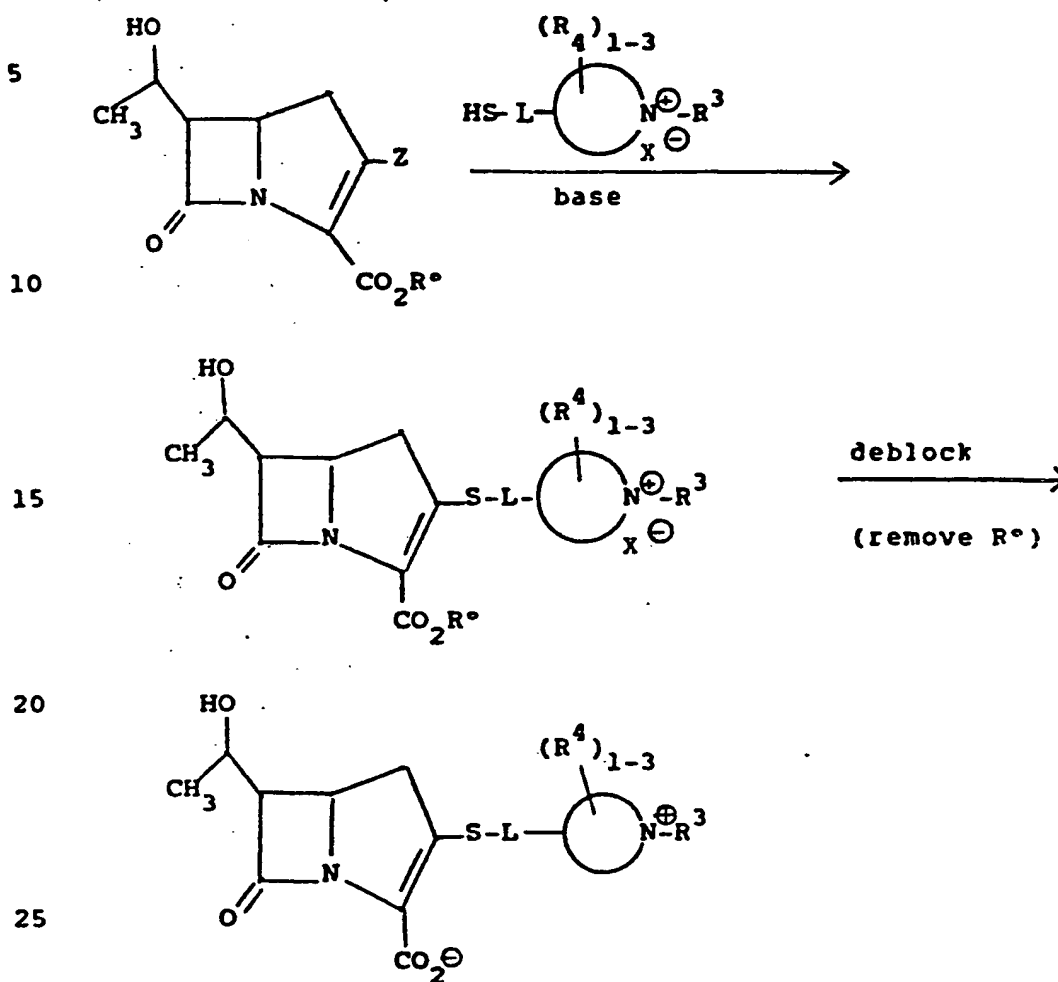
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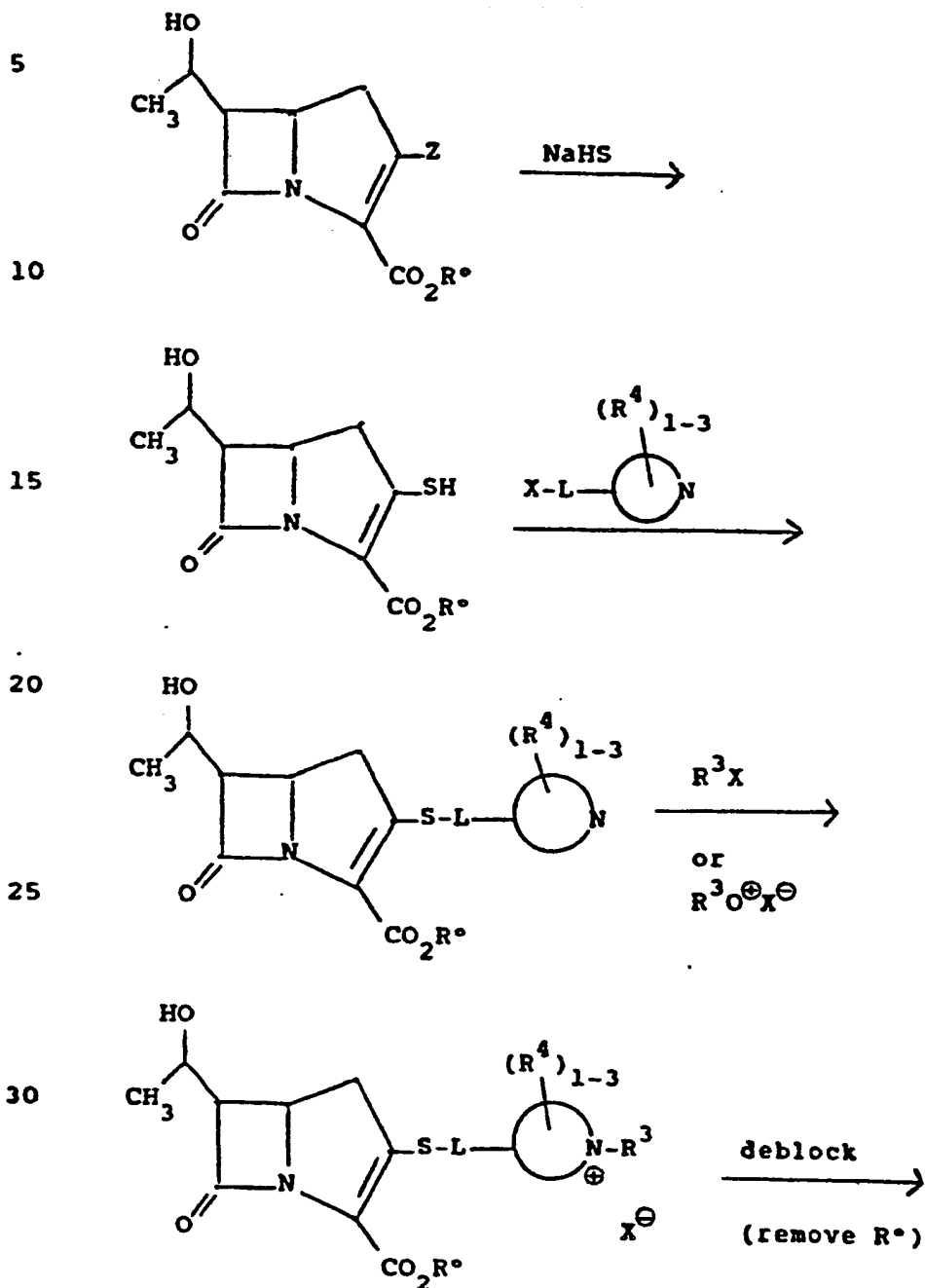
B. A second process is illustrated by the following set of equations:



wherein Z, X, L, R^0 , R^3 and R^4 are as defined above.

30 The difference between the above process and that earlier described is that the side chain moiety is alkylated with the group R^3 prior to addition to the carbapenem nucleus. The side chain addition step and deblocking are conducted as described above.

C. A third process is illustrated by the following set of equations:

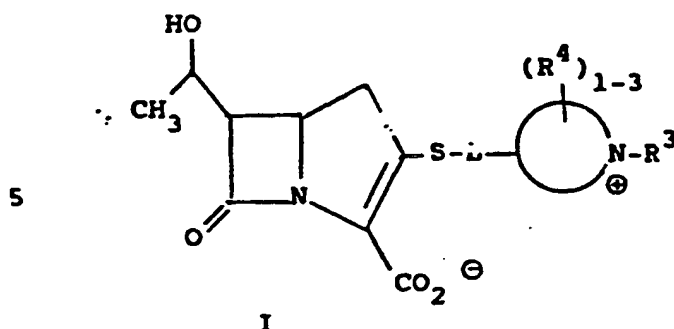


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10 wherein Z, X, L, R⁰, R³ and R⁴ are as previously defined.

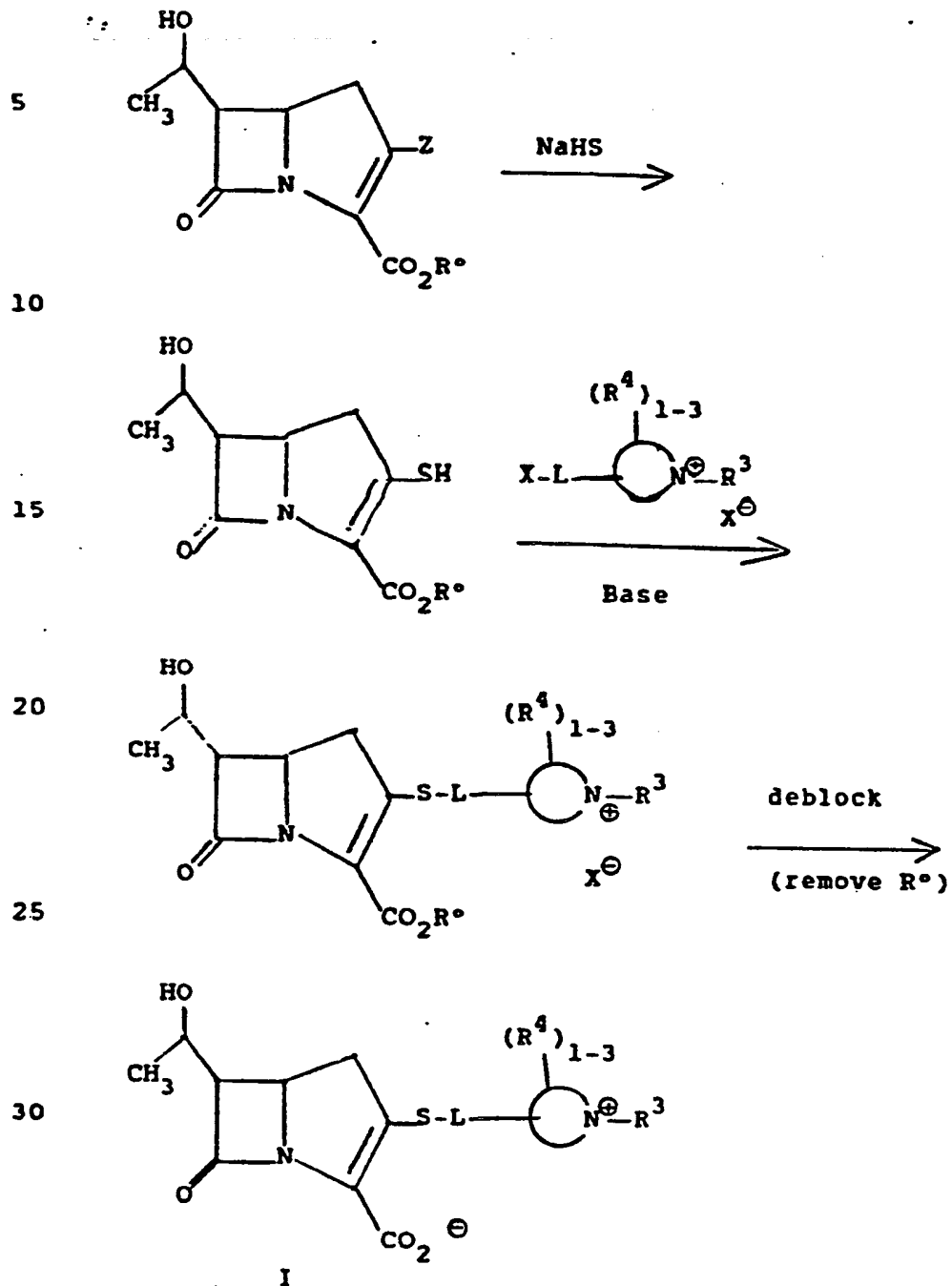
In this case the 2-mercapto intermediate is generated from the activated carbapenem upon exposure to sodium hydrosulfide in dimethylformamide or dimethylacetamide at a temperature of from -50°C to -20°C for a period of five minutes to one hour. The sulfur atom is alkylated in a solvent such as acetonitrile, dimethylformamide, dimethylacetamide or the like in the presence of a base such as N,N-diisopropylethylamine, triethylamine, 4-dimethylaminopyridine or the like at a temperature of from -40°C to 25°C for a period of from ten minutes to eight hours. The side chain alkylation, removal of R⁰ and purification of I is conducted as described above.

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D. A fourth process is illustrated by the following set of equations:



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wherein Z, X, R⁰, R³, and R⁴ are as previously defined.

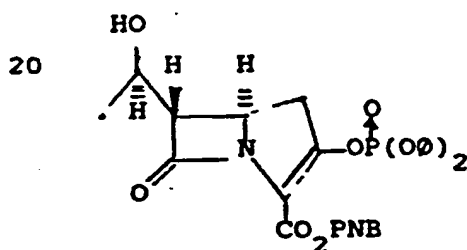
The difference between this process and that described in process C is that the side chain moiety is alkylated with the group R³ prior to addition to the carbapenem nucleus. The side chain addition step and the deblocking are conducted as described above.

The following examples illustrate the preparation of compounds of Formula I. The temperature is in degrees Celsius unless otherwise indicated.

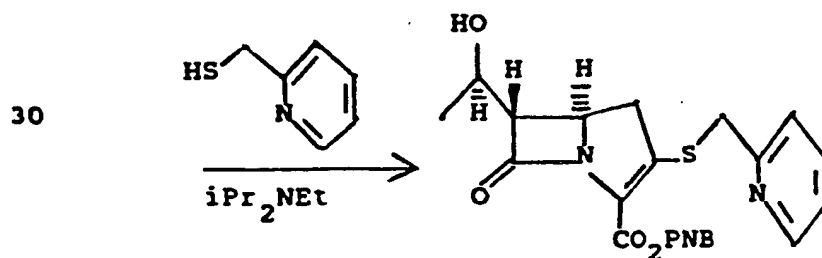
EXAMPLE 1

Step A.

Preparation of p-Nitrobenzyl (5R,6S)-6-(1(R)-hydroxyethyl)-2-(2-pyridylmethylthio)-carbapen-2-em-3-carboxylate 2.



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A solution of vinyl phosphate 1 (2.32 g. 4
mmoles) in anhydrous acetonitrile is cooled to -20°
(ice-methanol) under a nitrogen atmosphere and
treated with 2-mercaptomethylpyridine (0.554 ml, 5.0
5 mmoles) and diisopropylethylamine (0.871 ml, 5.0
mmoles). The resulting mixture is stirred at -20 to
-15° for 60 minutes during which time a precipitate
formed. The mixture is diluted with ethyl acetate
(16 ml) and aged at -15° to -5° for 30 minutes. The
10 precipitate is collected, washed with ice-cold ethyl
acetate and dried in vacuo to give the product (1.095
g) as a white solid.

The filtrate and washings are diluted with
ethyl acetate, washed with 0.1M pH 7 phosphate buffer
15 two times and brine, dried over magnesium sulfate,
filtered and concentrated to a semisolid. This
material is triturated with ethyl acetate and ether
two times and dried in vacuo to yield an additional
0.498 g of product. Total yield of 2 is 1.593 g, 87%.

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Step B.

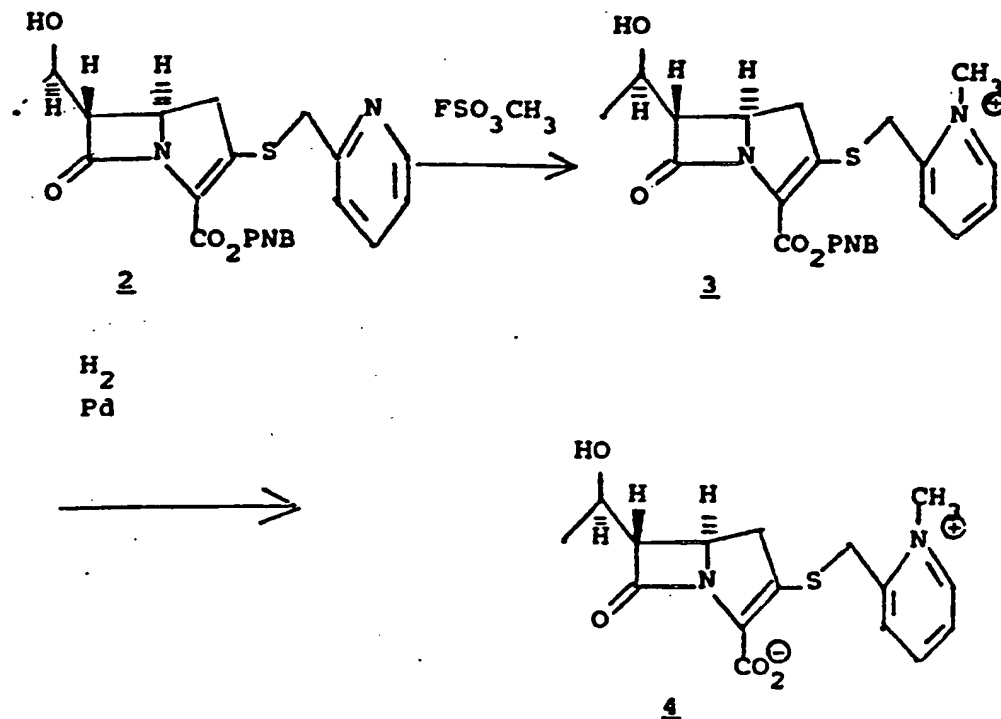
(Preparation of (5R,6S)-6-(1(R)-hydroxyethyl)-2-(1-methyl-2-pyridinium)methylthio-carbapen-2-em-3-carboxylate 4.)

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To a magnetically stirred solution of 2
 25 (0.853 g, 1.87 mmole) in 15.3 ml of dichloromethane
 is added methyl fluorosulfonate (0.160 ml, 1.97
 mmole) at room temperature. The reaction is followed
 by UV assay of removed aliquots of the solution.
 After two hours, a yellow oil separates and the UV
 30 absorbance at 318 nm of the dichloromethane layer
 drops to 4% of original. The upper layer is decanted
 and the lower layer washed two times with 5 ml

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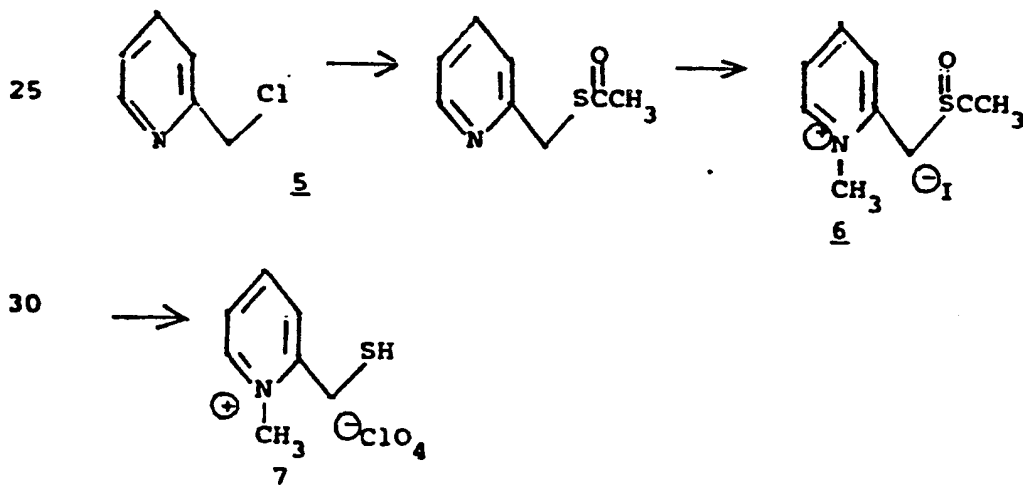
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portions of dichloromethane. The residual oil is assayed by UV for 3 then pumped to a foam in vacuo. The crude 3 thus produced is dissolved in a mixture of 6 ml of N,N-dimethylacetamide, 37 ml n-butanol, 19 ml ethyl acetate and 37 ml 0.5N N-methylmorpholine-HCl pH 7.0 buffer and 280 mg of 20% palladium hydroxide on carbon added. The mixture is hydrogenated at 42 psi with shaking for 70 minutes. At the end of this period, the mixture is removed, filtered through a prewashed celite bed with 5 to 10 ml water and the organic phase discarded. The aqueous phase is washed with 2 X 50 ml of dichloromethane and concentrated in vacuo to a volume of 23 ml. The solution of crude product is charged onto a 2.8 X 38 cm column of Dowex 50-X4 (Na⁺ cycle) at 5° and eluted with water. The eluate is monitored by UV and fractions containing the desired product are pooled, concentrated to 150 ml and lyophilized to yield 272 mg of final product 4.

20 Step C.

Preparation of 1-methyl-2-mercaptomethyl-pyridinium perchlorate 7.



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To a solution of 2-picolyyl chloride hydrochloride (5.00 g, 30.5 mmol) and potassium thioacetate (4.18 g, 36.6 mmol) in 50 ml N,N-dimethylformamide, triethylamine (4.25 ml, 30.5 mmol) is
5 added slowly to yield a pink solution. The mixture is heated to 80° and held there for 2 hours, after which time the solvent is removed in vacuo to yield a brown oil. The residue is taken up in ethyl acetate, washed with water and brine, dried over magnesium
10 sulfate, filtered and concentrated to yield crude 5 as a dark oil (5.0 g).

Thioester 5 (2.0 g, 12 mmol) is dissolved in 10 ml N,N-dimethylformamide under nitrogen and methyl iodide (7.5 ml, 120 mmol) is added dropwise. The
15 mixture is stirred 20 hours at room temperature, then the solvent is removed in vacuo to yield a brown powder which is triturated with dichloromethane, filtered and dried in vacuo to yield 2.21 g of 6 as a tan powder. Additional material (1.07 g) is obtained
20 by concentration of an aqueous extract of the dichloromethane wash from the trituration step. (nmr (D₂O) δ 2.49 (s); 4.42 (s); 7.9 to 9.0 (m)).

Pyridinium thioester 6 (102.7 mg, 0.33 mmol) is suspended in 0.63 ml 2N methanolic perchloric acid
25 and stirred at room temperature under nitrogen for 66 hours. The resulting tan suspension is filtered and the solid washed with ether to give 51.7 mg of thiol 7 as a tan powder (nmr (D₂O) δ 4.23 (s); 4.43 (s), 7.8 to 8.6 (m)).

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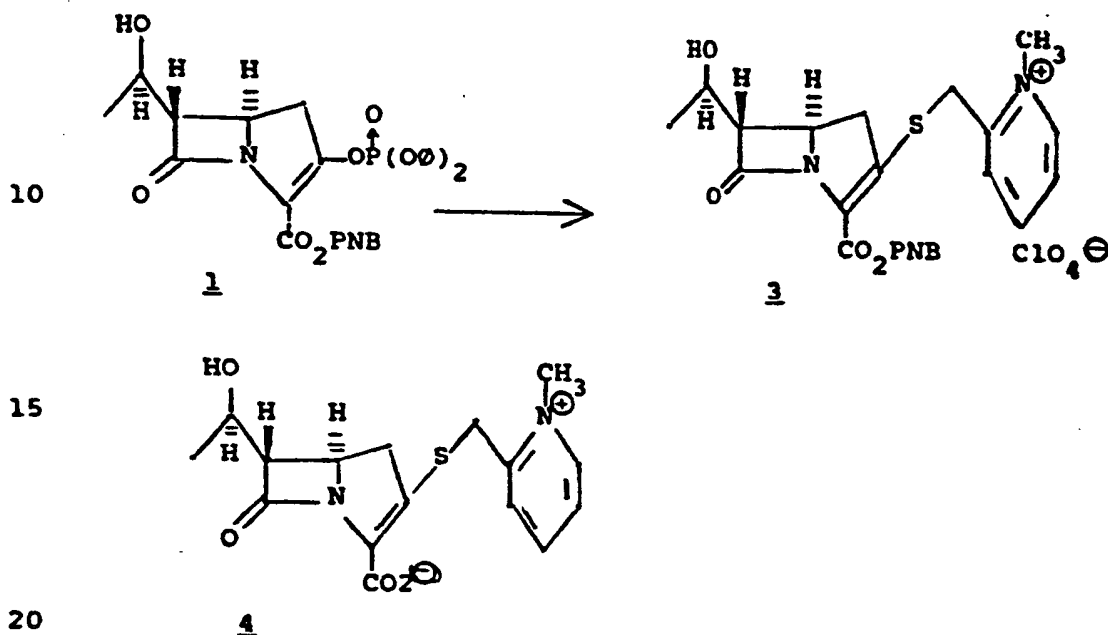
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Step D

Preparation of (5R,6S)-6-(1(R)-hydroxyethyl)-2-(1-methyl-2-pyridinium)methylthio-carbapen-2-em-3-carboxylate 4.

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To a solution of vinyl phosphate 1 (58 mg, 0.1 mmol) and thiol 7 (34.9 mg) in 0.32 ml of N,N-dimethylacetamide at -20° under nitrogen is added N,N-diisopropylethylamine (34.8 µl, 0.2 mmol). The mixture is aged 25 minutes at -20° then transferred directly to a hydrogenation vessel with 1.9 ml i-propanol, 1.0 ml ethyl acetate and 1.9 ml water. Phosphate buffer (pH 7, 0.1M, 1.0 ml) and 20% palladium hydroxide on carbon (15 mg) is added and the mixture hydrogenated at 46 psi for two hours. The catalyst is removed by filtration and the filtrate diluted with 5 ml ethyl acetate and 5 ml

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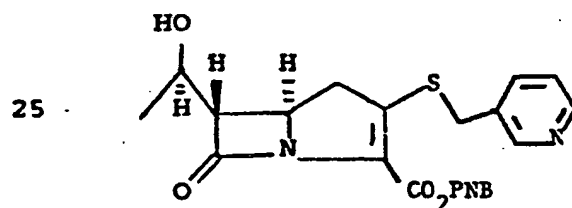
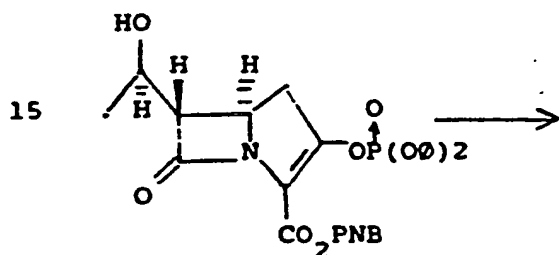
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water. The aqueous phase is separated, washed with ethyl acetate, concentrated to ca. 1 ml in vacuo and the product purified by chromatography on Dowex 50 -X4 (Na^+) as described above to yield 6.3 mg of product 4.

EXAMPLE 2Step A.

Preparation of p-Nitrobenzyl (5R,6S)-6-(1-R-hydroxy-ethyl)-2-(3-pyridylmethylthio)-carbapen-2-em-3-carboxylate 8.



To a solution of p-nitrobenzyl (5R,6S)-6-(1R-hydroxyethyl)-2-diphenylphosphonoxy-carbapen-2-em-3-carboxylate 1 (116 mg) in acetonitrile (0.3 ml)

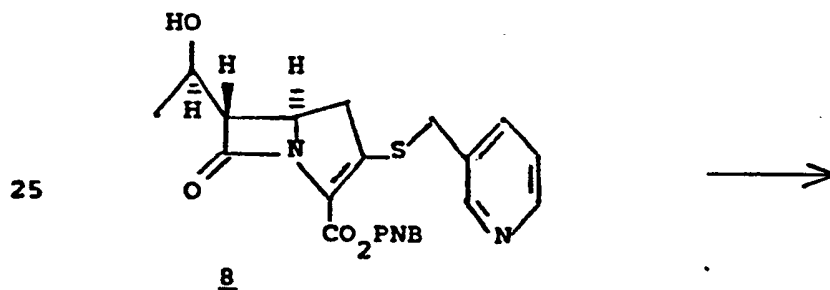
cooled in an ice-bath, is added diisopropylethyl-
amine (35 ml) and 3-mercaptomethylpyridine (25 μ l).
A precipitate forms within a few minutes. After one
hour the mixture is diluted with methylene chloride
5 and filtered. The filter cake is washed with
methylene chloride and dried by suction leaving
substantially pure p-nitrobenzyl (5R,6S)-6-(1-R-
hydroxyethyl)-2-(3-pyridylmethylthio) carbapen-2-em-
3-carboxylate (52 mg). The combined filtrates are
10 washed twice with pH7 phosphate buffer, dried over
anhydrous magnesium sulfate and evaporated to give an
additional 17 mg of crystalline product 8. Total
yield 77%. TLC, silica gel, 5% MeOH/CHCl₃. R_f =
0.21.

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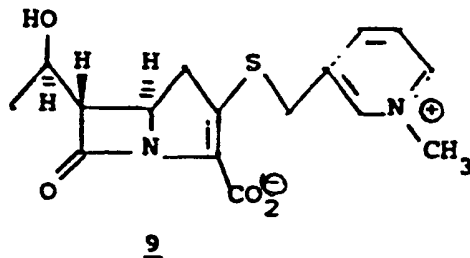
Step B.

Preparation of (5R,6S)-6-(1-R-hydroxyethyl)-2-
(1-methyl-3-pyridiniummethylthio)-carbapen-2-em-
3-carboxylate 9.

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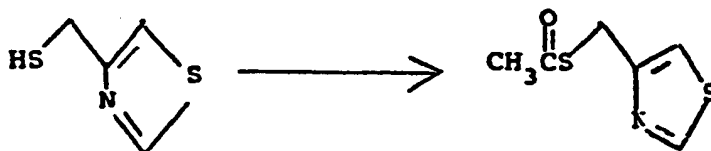
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To a suspension of p-nitrobenzyl (5R,6S)-6-(1-(R)-hydroxyethyl)-2-(3-pyridylmethylthio)-carbapen-2-em-3-carboxylate (61 mg) in methylene chloride (2 ml) is added methyl fluorosulfonate (12 μ l). The mixture is stirred at room temperature for one hour. The solid changes appearance without dissolving. The solvent is evaporated in a stream of nitrogen leaving a powder consisting of p-nitrobenzyl (5R,6S)-6-(1-(R)-hydroxyethyl)-2-(1-methyl-3-pyridiniummethylthio)-carbapen-2-em-3-carboxylate fluorosulfonate salt. This is dissolved in a mixture of 8 ml THF and 8 ml of 0.05M pH 7 phosphate buffer and hydrogenated in the presence of 40 mg of 10% Pd/C catalyst at 45 psi for 2 hours. The catalyst is filtered and the filtrate is extracted once with 30 ml of ether. The aqueous solution is adjusted to pH 6.8 by the addition of solid sodium bicarbonate and applied to an ice-water jacketed column (1.5 X 24 cm) of Dowex 50, Na⁺ cycle resin (200 to 400 mesh). The column is eluted with de-ionized water taking 20 ml fractions. Fractions 6 to 10 are combined, concentrated to 10 ml and lyophilized giving the titled product 2 as a cream colored powder (50 mg). U.V. λ_{max} at 265 and 296 nm of equal intensity E₁ 233, 86% NH₂OH extract. NMR (D₂O) δ 1.26 (d, J=6.5 Hz), 3.02 (dd, J=9 and 18 Hz), 3.15 (dd, J=10 and 18 Hz), 3.39 (dd, J=2.8 and 6Hz), 4.2 (m), 4.3 (ABq), 4.4 (s), 8.04, 8.57, 8.9 (ar).

EXAMPLE 3Step A.Preparation of 4-(acetylthiomethyl)thiazole 10.

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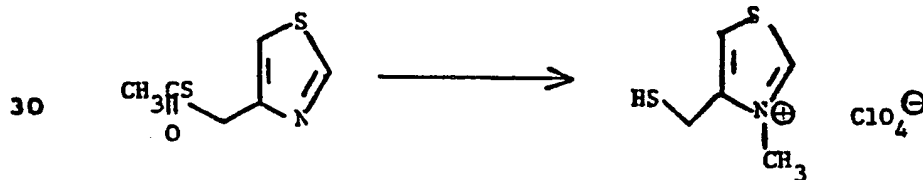
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To an ice-cooled solution of 4-thiomethylthiazole (2g, 0.0152 mole) in methylene chloride (20 ml) is added triethylamine (2.1 ml, 0.0152 mole) and acetyl chloride (1.08 ml, 0.0152 mole). A precipitate forms immediately and after 10 minutes the mixture is filtered, washed twice with pH 7 phosphate buffer, dried over anhydrous magnesium sulfate and evaporated. Distillation of the residue at 7mm/117-119°C gave 2.23 g of the title compound as a clear liquid. 86% yield.

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Step B.Preparation of 3-methyl-4-thiomethylthiazolium perchlorate 11.

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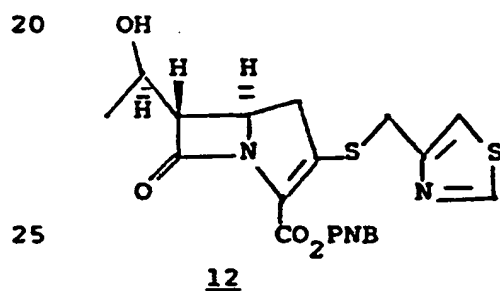
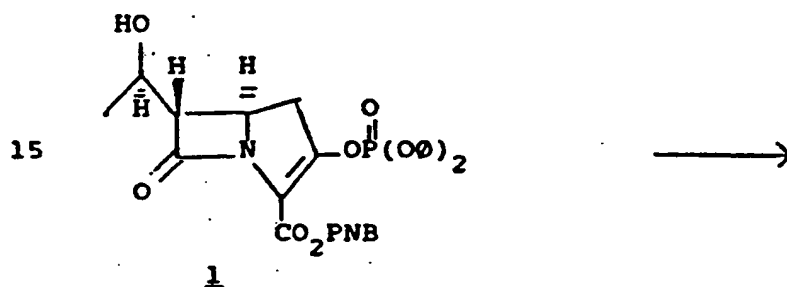
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To an ice-cooled solution of
4-acetylthiomethylthiazole (1g, 0.0058 mole) in
acetonitrile (5 ml) is added methylfluorosulfonate
(0.49 ml, 0.0058 mole) dropwise. The reaction is
5 warmed to room temperature and gives 1.5 g of a white
solid upon treatment with ether. The solid is
suspended in methanolic 2N HClO₄ and slowly
dissolves over 18 hours at room temperature. The
title compound (0.23g, 84% yield) is collected upon
10 addition of ether.



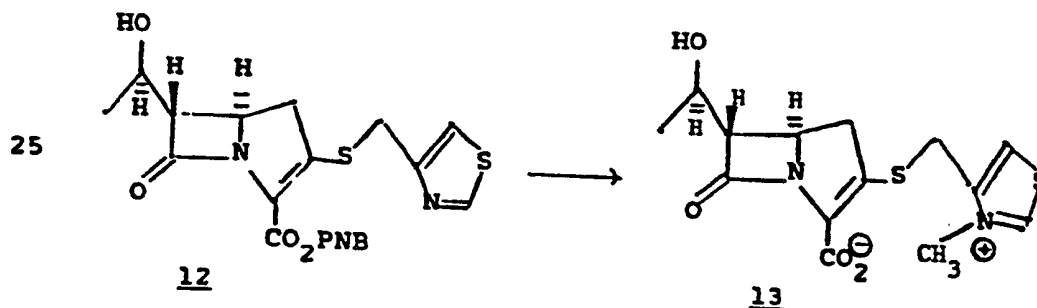
Step C.

Preparation of p-nitrobenzyl (5R,6S)-6-(1-R-hydroxy-ethyl)-2-(4-thiazolylmethylthio)-carbapen-2-em-3-carboxylate 12

5 p-Nitrobenzyl (5R,6S)-6-(1-R-hydroxyethyl)-
2-diphenylphosphonoxy-carbapen-2-em-3-carboxylate 1
10 (0.406 g. 0.70 mmoles) is dissolved in anhydrous
acetonitrile (3 cc) and is cooled in an ice-bath
under N₂. Diisopropylethylamine (122 μ l, 0.70
mmoles) and 4-thiomethylthiazole (70 μ l, 0.70 mmoles)
are added simultaneously and a precipitate forms
within a few minutes. After 30 minutes the mixture
is filtered and the collected solid is washed with
ethyl acetate giving 0.21 g of the title compound 12.
15 yield 69%.

Step D.

Preparation of (5R,6S)-6-(1-R-hydroxyethyl)-2-(3-methyl-4-thiazoliummethylthio)carbapen-2-em-3-carboxylate 13.



30 To an ice-cooled suspension of p-nitrobenzyl (5R,6S)-6-(1-R-hydroxyethyl)-2-(4-thiazolylmethylthio)-carbapen-2-em-3-carboxylate 12 (.45 g, 0.1 mmoles) in acetonitrile (1cc) is added methyl

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fluorosulfonate (8.5 μ l, 0.1 mmoles). The mixture is warmed to room temperature and the solid gradually dissolved over 30 minutes. The solvent is then evaporated in a stream of nitrogen and the resulting semi-solid is dissolved in tetrahydrofuran (8 ml), pH 6.5 phosphate buffer (4 ml) and H_2O (4 ml) and is hydrogenated for 2 hours at 45 psig in the presence of 10% Pd/C (50 mg). The catalyst is filtered and the filtrate is washed once with ether. The aqueous layer (pH 6.2) is concentrated to 5cc and is placed on a column (27.5 x 1.5 cm) of Dowex 50W-X4 200-400 mesh sodium-cycle resin. The column is eluted with de-ionized water and the fractions between 100 ml and 270 ml are collected, concentrated to 8 cc and lyophilized to give 10 mg of 13 as a light yellow powder.

UV (H_2O) λ max at 245 and 295.

NMR (selected resonances) (D_2O) δ 1.28 (3H, d, J=6.5Hz), 3.42 (1H, dd, J=2.8, 6.1 Hz), 4.25 (3H, s).

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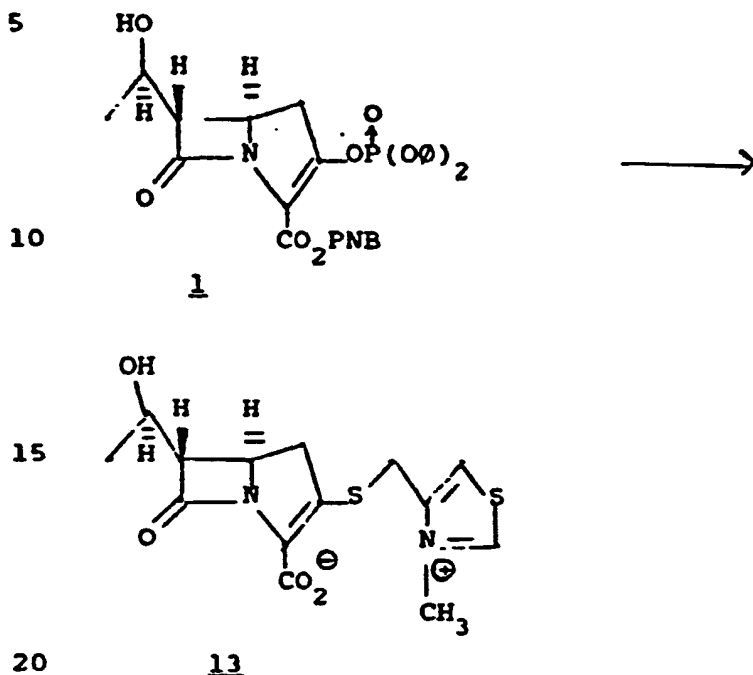
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Step E.

(5R,6S)-6-(1-R-hydroxyethyl)-2-(3-methyl-4-thiazolium methylthio)-carbapen-2-em-3-carboxylate 13.



A solution of p-nitrobenzyl (5R,6S)-6-(1-R-hydroxyethyl)-2-diphenylphosphonoxy-carbapen-2-em-3-carboxylate 1 (7.43 g, 0.0128 mole) in N,N-dimethylacetamide (38 ml) is cooled to -20°C in an ethylene glycol/H₂O/dry ice mixture and is treated with 3-methyl-4-thiomethylthiazolium perchlorate 11 (3.13 g, 0.0128 mole) and diisopropylethylamine (2.2 g, 0.0128 mole). After 30 minutes the reaction mixture is added to butanol (200 cc), ethyl acetate (120 cc), de-ionized water (200 cc) and pH 6.8 0.5N N-methylmorpholine buffer (350 cc) and is hydrogenated for 2 hours in the presence of 5 g of

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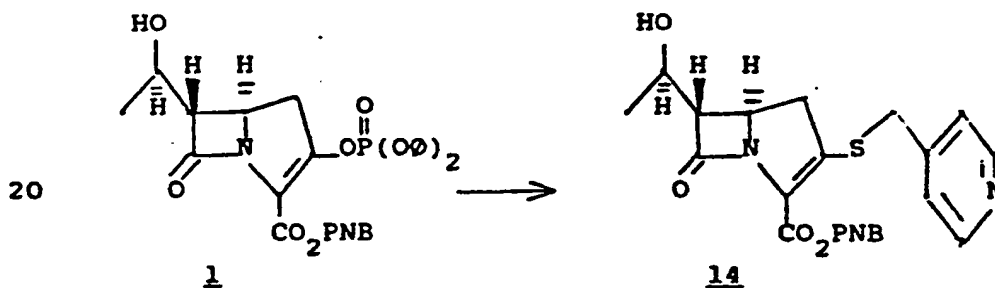
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20% Pd(OH)₂/C. The catalyst is filtered and the filtrate is washed several times with methylene chloride. The pH is adjusted to 6.7 with solid sodium bicarbonate and the aqueous layer is placed on a (9.75 X 23 cm) Dowex 50W-X4 200-400 mesh sodium cycle column. The column is eluted with de-ionized water and a center-cut fraction is taken, concentrated and lyophilized to give 3.1g of the title compound 13 as a light yellow powder.

EXAMPLE 4

Step A: Preparation of p-Nitrobenzyl (5R,6S)-2-(4-pyridylmethylthio)-6[1(R)-hydroxyethyl]-carbapen-2-em-3-carboxylate (14)

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A suspension of p-nitrobenzyl (5R,6S)-2-(diphenylphosphono)oxy-6[1(R)-hydroxyethyl]-carbapen-2-em-3-carboxylate (2.50 g, 4.31 mmol) and 4-pyridine-methanethiol hydrochloride (0.73 g, 4.52 mmol) in anhydrous acetonitrile (9.0 ml) was cooled in an ice-water bath and treated with N,N-diisopropylethylamine (1.6 ml, 9.05 mmol). A solution formed which rapidly developed into a suspension. After stirring at 0° for 30 minutes, the suspension was filtered and the white solid washed with cold

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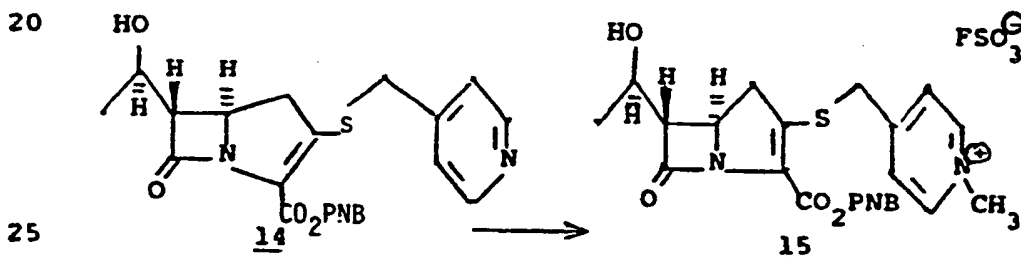
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acetonitrile and vacuum dried to provide the title compound 14 (1.71 g).

- 5 NMR (DMSO d_6) δ 1.13 (d, $J=6.3$ Hz, CH_3CH), 3.1-3.4 (m, $CHCH_2$, H6), 3.95 (sextet, J 6 Hz, $CHOH$), 4.13 (dt, $J=9.4$, 2.7 Hz, H5), 4.25 (ABq, $J=14.2$ Hz, SCH_2), 5.09 (d, $J=4.9$ Hz, $CHOH$), 5.38 (ABq, $J=14.2$ Hz, CH_2Ar), 7.41 (dd, $J=4.5$, 1.5 Hz, pyr), 7.70 (d, $J=8.8$ Hz, Ar), 8.24 (d, $J=8.8$ Hz, Ar), 8.55 (dd, $J=4.5$, 1.5 Hz, pyr).
- 10 IR (Nujol) 3150, 1785, 1680, 1595 cm^{-1}
 UV (p-dioxane) λ_{max} 319 nm (ϵ 12,700),
 265 nm (ϵ 12,800)
 m.p. 159-160° (dec)

- 15 Step B: Preparation of p-Nitrobenzyl (5R,6S)-2-(4-methyl-4-pyridiniummethylthio)-6[1(R)-hydroxyethyl]carbapen-2-em-3-carboxylate fluoro-sulfonate (15)



- A suspension of p-nitrobenzyl (5R,6S)-2-(4-pyridiniummethylthio)-6[1(R)-hydroxyethyl]carbapen-2-em-3-carboxylate 14 (1.70 g, 3.73 mmol) in
- 30 dichloromethane (37 ml) was cooled in an ice-water bath and treated with methyl fluorosulfonate (0.32 ml, 3.93 mmol). After stirring at 0° for 1 hour, the reaction had deposited a viscous yellow oil. The

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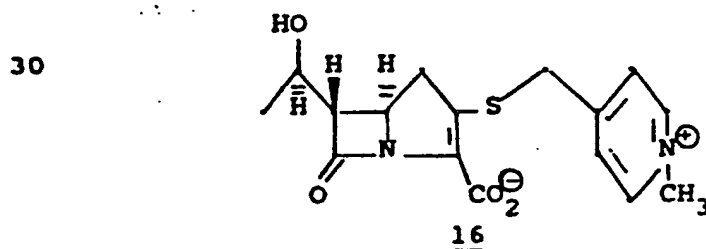
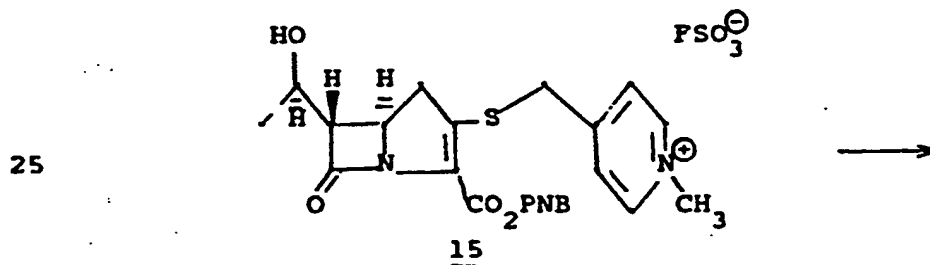
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dichloromethane was decanted and the residue washed with dichloromethane and briefly pumped under vacuum. The residue was triturated with i-propanol to give a yellow solid which was recovered by
5 filtration and vacuum dried to afford the title compound 15 (2.08 g).

NMR (DMSO- d_6) δ 1.12 (d, $J=6.2\text{Hz}$, CH_3CH), 3.12 (dd, $J=18.6$, 8Hz , CHCH_AH_B), 3.3 (dd, $J=18.6$, 10.0Hz , CHCH_AH_B), 3.30 (dd, $J=6.3$, 3Hz , H_6), 3.95
10 (p, $J=6\text{Hz}$, CHOH), 4.11 (dt, $J=9.3\text{Hz}$, H_5), 4.31 (s, NCH_3), 4.50 (s, CH_2 , Pyr), 5.38 (ABq, $J=14.2\text{Hz}$, CH_2Ar), 7.71 (d, $J=8.7\text{Hz}$, ArNO_2), 8.13 (d, $J=6.6\text{Hz}$, Pyr), 8.25 (d, $J=8.7\text{Hz}$, ArNO_2), 8.91 (d, $J=6.6\text{Hz}$, Pyr).

15 IR (Nujol) 3520, 1765, 1690, 1645, 1600 cm^{-1}
UV (MeOH) λ_{max} 314 ($\epsilon 11,000$), 262 ($\epsilon 13,200$)

20 Step C: Preparation of p-Nitrobenzyl (5R,6S)-2-(1-methyl-4-pyridiniummethylthio)-6[1(R)-hydroxyethyl]carbapen-2-em-3-carboxylate (16)



A solution of p-nitrobenzyl (5R,6S)-2-(1-methyl-4-pyridiniummethylthio)-6[1(R)-hydroxyethyl]-carbapen-2-em-3-carboxylate 15 (1.90 g, 3.34 mmol) in N-ethylpyrrolidinone (19 ml) was mixed with n-butanol (66 ml), ethyl acetate (32 ml), water (66 ml), and 0.5M pH 7.0 N-methylmorpholine-hydrochloric acid buffer. The resulting two phase mixture was treated with 20% palladium hydroxide on carbon (1.9 g) and hydrogenated on a Parr shaker at 45 psi for 75 minutes. The mixture was filtered through a celite pad and the organic phase which separated was discarded. The aqueous phase was washed twice with dichloromethane and concentrated under vacuum to ca. 48 ml. This solution was charged onto a column of Dowex 50W-X4 resin (sodium form, 200-400 mesh, 5.0 cm diameter x 30 cm) which was eluted with water in a cold room at 20 ml fractions/1.0 minute. Fractions 105-180 which contained product were combined, concentrated under vacuum and lyophilized to afford the title compound 16 (189 mg) as a light tan-colored fluff.

NMR (D_2O) δ 1.25 (d, $J=6.3\text{Hz}$, CH_3CH), 3.02 (dd, $J=17.3$, 8.7Hz , CHCH_AH_B), 3.07 (dd, $J=17.3$, 9.5Hz , CHCH_AH_B), 3.37 (dd, $J=5.9$, 2.7Hz , H_6), 4.11 (dt, $J=9.2$, 2.4Hz , H_5), 4.20 (p, $J=6\text{Hz}$, CHOH), 4.36 (s, NCH_3), 8.06 (d, $J=6.7\text{Hz}$, pyr), 8.71 (d, $J=6.7\text{Hz}$, pyr).

IR (Nujol) 3350 (br), 1758, 1641, 1587 cm^{-1}

UV (water) λ_{max} 297 nm ($\epsilon 7,710$), 258

($\epsilon 6,850$); (water + $\text{NH}_2\text{OH}\cdot\text{HCl}$)
extinguished λ_{max} 296 nm ($\epsilon 6,850$)

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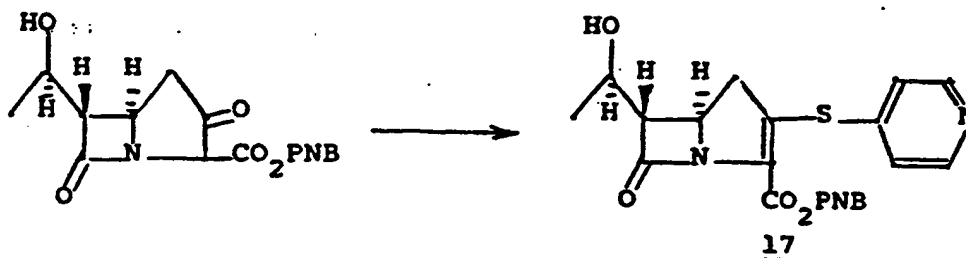
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EXAMPLE 5

Step A: Preparation of p-Nitrobenzyl (5R,6S)-2-(4-pyridylthio)-6[1(R)-hydroxyethyl]carbapen-2-em-3-carboxylate (17)

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A solution of p-nitrobenzyl (5R,6S)-6[1(R)-hydroxyethyl]-2-oxocarbapenam-3(R)-carboxylate (200 mg, 0.574 mmol) in acetonitrile (0.60 ml) was treated at ice-water bath temperature with diphenylchlorophosphate (0.125 ml, 0.603 mmol) and N,N-diisopropylethylamine (0.119 ml, 0.683 mmol). After stirring at 0° for 25 minutes, the reaction was treated with additional N,N-diisopropylethylamine (0.110 ml, 0.612 mmol) and a solution of 4-mercaptopyridine (95.6 mg, 0.816 mmol) in N,N-dimethylformamide (0.7 ml) and acetonitrile (2.2 ml). The reaction solution was stirred 3.5 hours at 0° and diluted with ethyl acetate. The solution was washed with 5% aqueous sodium bicarbonate solution, dried over anhydrous MgSO₄, filtered, and evaporated under vacuum to provide the title compound as a foam (286 mg).

The crude product was chromatographed on a column of silica gel (29 g) eluted with 10% ethanol in ethyl acetate. Fractions containing compound 17 were combined and concentrated to a foam (147 mg) under vacuum.

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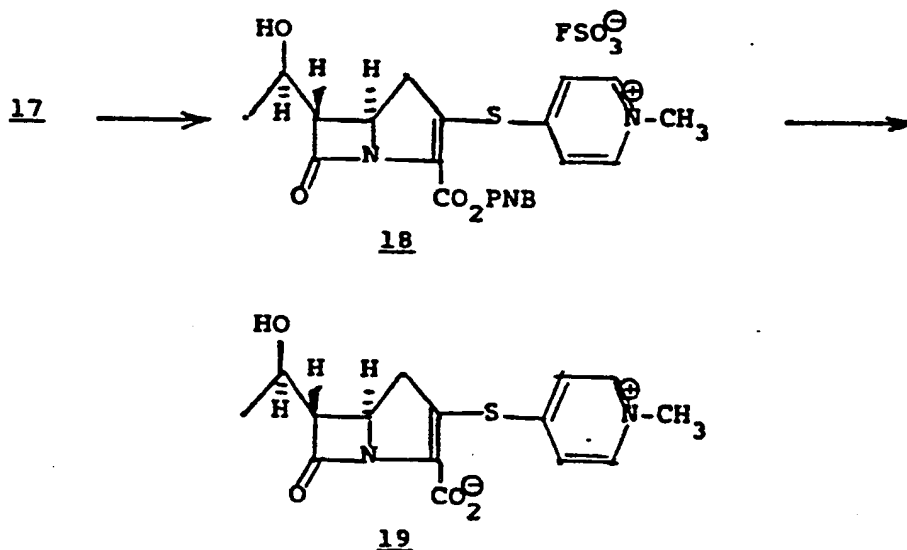
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NMR (DMSO- d_6) δ 1.09 (d, $J=6.5$ Hz, CH_3CH), 2.82 (dd, $J=10.1, 18.0$ Hz, CHCH_ACH_B), 3.05 (dd, $J=8.3, 18.0$ Hz, CHCH_ACH_B), 3.38 (dd, $J=3.0, 5.8$ Hz, H6), 3.96 (sextet, $J=6$ Hz, CHOH), 4.15 (dt, $J=3.0, 8$ Hz, H5), 5.06 (d, $J=5.0$ Hz, CHOH), 5.46 (ABq, $J=14.0$ Hz, CH_2Ar), 7.65 (dd, $J=1.4, 4.5$ Hz, pyr), 7.77 (d, $J=8.9$ Hz, ArNO_2), 8.30 (d, $J=8.9$ Hz, ArNO_2), 8.65 (dd, $J=1.4, 4.5$ Hz, pyr).

IR (CH_2Cl_2) 1770, 1718, 1690 cm^{-1}

ms 441 (M^+), 330 ($\text{M}^+ - \text{C}_5\text{H}_5\text{NS}$), 246 (330 - $\text{C}_4\text{H}_4\text{O}_2$), 111 (246 - $\text{C}_7\text{H}_5\text{NO}_2$).

Step B: Preparation of p-Nitrobenzyl (5R,6S)-2-(4-pyridylthio)-6[1(R)-hydroxyethyl]carbapen-2-em-3-carboxylate (19)



A solution of p-nitrobenzyl (5R,6S)-2-(4-pyridylthio)-6[1(R)-hydroxyethyl]-carbapen-2-em-3-carboxylate 17 (70 mg, 0.17 mmol) in dichloromethane

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- (3.0 ml) was stirred in an ice-water bath and treated with methyl fluorosulfonate (21 μ l, 0.26 mmol). After stirring 15 minutes, the cold solution was mixed with ether (10 ml) and filtered. The recovered quaternary salt 18 was dissolved in tetrahydrofuran (3.5 ml) and aqueous 0.1N pH 2.1 phosphate buffer (3.5 ml). The solution was treated with 10% palladium on carbon and hydrogenated on a Parr shaker at 45 psi for 1 hour. The catalyst was removed by centrifugation and the decanate was diluted with water (2 ml), and washed with ethyl acetate. The aqueous phase was briefly concentrated under vacuum to ca. 5 ml and charged onto a column of Dowex 50W-X4 (sodium form, 200-400 mesh, 1.5 x 36 cm). The column was eluted with water in a cold room at 6.0 ml fractions/2.5 minutes. Fractions 27 to 47 which contained product were combined, concentrated under vacuum, and lyophilized to afford the title compound 19 (7 mg).
- 20 NMR (D_2O) δ 1.30 (d, $J=6.5$ Hz, $CHCH_3$), 3.08 (dd, $J=8.9, 17.8$ Hz, $CHCH_{AB}$), 3.22 (dd, $J=10.0, 17.8$ Hz, $CHCH_{AB}$), 3.64 (dd, $J=3.1, 6$ Hz, H6), 4.25 (s, N- CH_3), 4.30 (p, $J=6$ Hz, $CHOH$), 4.43 (dt, $J=3.1, 9.5$ Hz, H5), 7.83 (d, $J=7.5$ Hz, pyr), 8.50 (d, $J=7.5$ Hz, pyr).
- 25 UV (water) λ_{max} 303 nm (ϵ 9,820).

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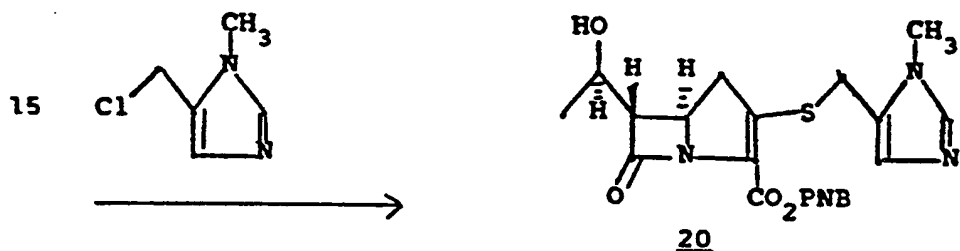
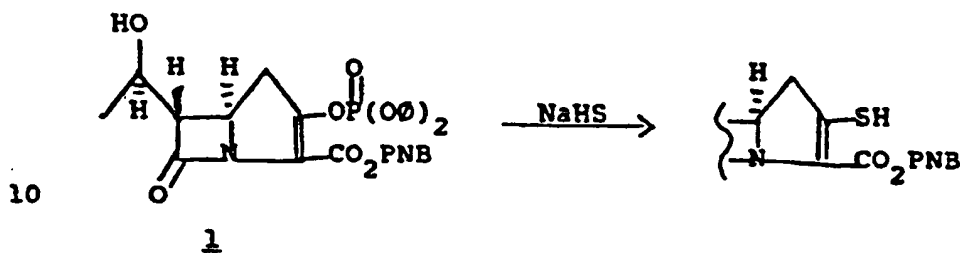
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EXAMPLE 6

Step A: Preparation of p-Nitrobenzyl (5R,6S)-6[1(R)-hydroxyethyl]2-[(1-methyl-5-imidazolyl)methylthio]carbapen-2-em-3-carboxylate (20)

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20 A solution of vinyl phosphate 1 (674 mg, 1.16 mmol) in anhydrous N,N-dimethylformamide (DMF, 3.9 ml) was cooled in a dry ice-acetonitrile bath (-40°C) under a N₂ atmosphere and treated dropwise over 2 minutes with a solution of sodium hydrogen sulfide (68.4 mg, 1.22 mmol) in DMF (2 ml). The reaction mixture was treated with N,N-diisopropylethylamine (0.647 ml, 3.72 mmol), stirred at -40°C for 20 minutes, then treated dropwise with a solution of 1-methyl-4-chloromethylimidazole hydrochloride (203.6 mg, 1.22 mmol) in DMF (2.4 ml). After stirring an additional 20 minutes at -40°C, the reaction mixture was diluted with ethyl acetate (100 ml), washed with water (4 x 100 ml) and brine, dried

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with MgSO_4 , filtered, and evaporated in vacuo to give a yellow-brown solid (367 mg). This material was triturated with 1:1 ethyl acetate-ether and dried in vacuo to afford the title compound 20 (250 mg,

5 47%) as a yellow-brown solid.

IR (Nujol) ν_{max} 1769, 1690, 1517, 1333 cm^{-1} ;

UV (dioxane) λ_{max} 319 nm (ϵ 12,600), 267 (11,900);

NMR (CDCl_3) δ 1.37 (d, $J=6.3\text{Hz}$, CH_3CHOH), 3.14

(dd, $J=17.8$ and 8.6Hz , CHCHaHb), 3.21 (dd, $J=2.7$ and

10 6.7Hz, H6), 3.42 (dd, $J=17.8$ and 9.7Hz , CHCHaHb),

3.68 (s, NCH_3), 4.03, 4.12 (ABq, $J=14.6\text{Hz}$, SCH_2),

4.25 (m, H5 and CH_3CHOH), 5.23, 5.50 (ABq,

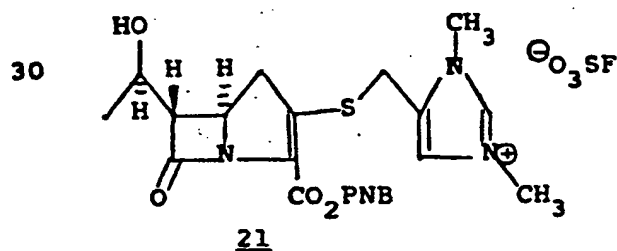
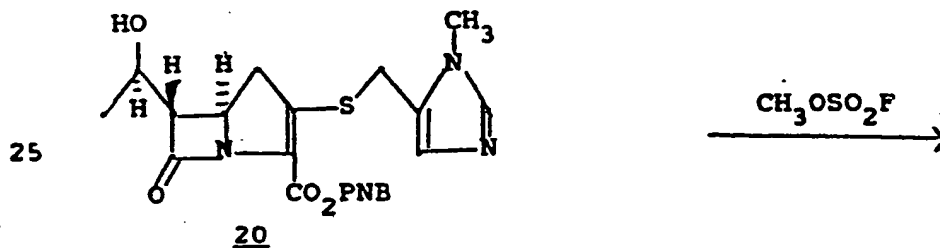
$J=13.8\text{Hz}$, CH_2Ar), 7.00 (s, imidazole-H), 7.47 (s,

imidazole-H), 7.65 (d, $J=8.7\text{Hz}$, 2 ArH), 8.22 (d,

15 $J=8.7\text{Hz}$, 2ArH).

Step B: Preparation of p-Nitrobenzyl (5R,6S)-6[1(R)-hydroxyethyl]2-[(1,3-dimethyl-4-imidazolium)-methylthio]carbapen-2-em-3-carboxylate fluoro-

20 sulfate (21)



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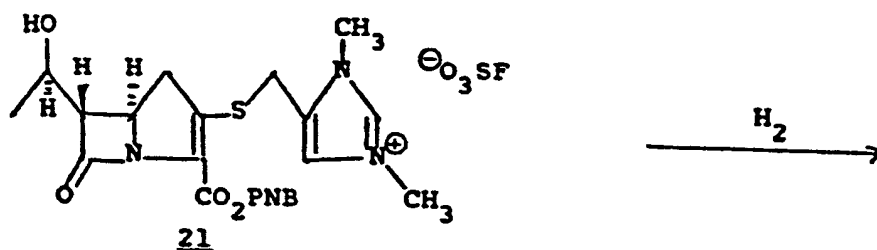
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A solution of carbapenem derivative 20 (223.6 mg, 0.49 mmol) in anhydrous methylene chloride (10 ml) was cooled in an ice-bath and stirred under a nitrogen atmosphere while a solution of methyl
 5 fluorosulfate (0.042 ml, 0.52 mmol) in methylene chloride (2 ml) was added dropwise over 5 minutes. A gummy precipitate formed which, on continued stirring at 0°C, gave way to a fine, cream colored solid. After 30 minutes, the solid was collected, washed
 10 with methylene chloride (2 x 10 ml), and dried in vacuo to give 21 (228 mg) as a cream colored powder. IR (Nujol) ν_{max} 1767, 1691, 1620, 1290 cm^{-1} ; UV (10:1 dioxane-water) λ_{max} 316 nm (ϵ 12,500), 271 (11,300).

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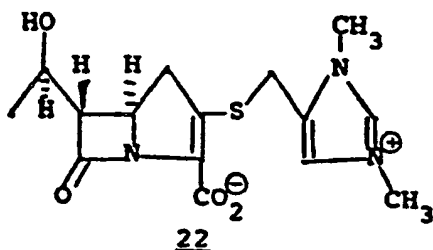
Step C: Preparation of (5R,6S)-6[1(R)-hydroxyethyl]-2-[(1,3-dimethyl-4-imidazolium)methylthio]-carbapen-2-em-3-carboxylate (22)

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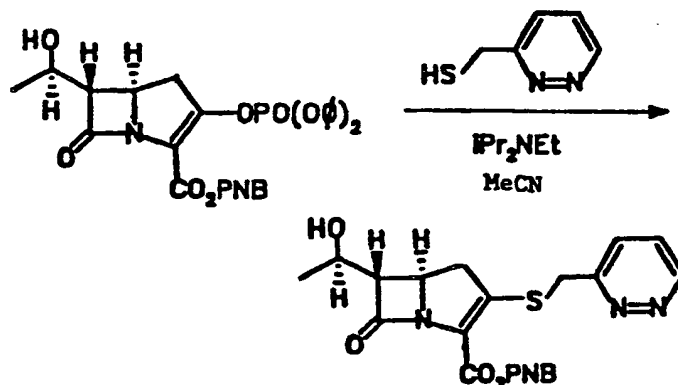
The imidazolium salt 21 (221 mg, 0.386 mmol) was taken up in a mixture of n-butanol (20 ml), ethyl acetate (10 ml), water (20 ml), and 0.5M pH 6.8 N-methylmorpholine-hydrochloric acid buffer (10 ml).
5 treated with 20% palladium hydroxide on carbon (100 mg), and hydrogenated at 45 psi for one hour. The mixture was filtered through a celite pad to remove the catalyst which was washed with additional water. The aqueous portion of the filtrate was washed three
10 times with methylene chloride, concentrated in vacuo to ca. 3 ml, and loaded onto a column of Dowex 50W-X4 resin (sodium form, 200-400 mesh, 2.5 x 34 cm) which was eluted with de-ionized water in a cold room at 400 drop fractions every 5.1 minutes. The product
15 containing fractions (23-32, 242 ml) were located by uv, concentrated in vacuo, and lyophilized to yield the title compound 22 (69 mg) as a white, amorphous solid.

IR (Nujol) ν_{max} 3400 (br), 1750, 1590 cm^{-1} ;
20 uv (0.05M pH 7.0 MOPS) λ_{max} 297 nm (96% NH_2OH extinguished, $\epsilon_{\text{ext.}}$ 7,900);
NMR (D_2O) δ 1.28 (d, $J=6.4\text{Hz}$, CH_3CHOH), 3.09 (dd, $J=8.6$ and 17.5Hz , CHCHaHb), 3.24 (dd, $J=9.5$ and 17.4Hz , CHCHaCHb), 3.42 (dd, $J=2.6$ and 6.0Hz , H6),
25 3.85 (s, NCH_3), 3.86 (s, NCH_3), 4.07, 4.21 (ABq, $J=15.5\text{Hz}$, SCH_2), 4.18 (m, H5), 4.23 (pentet, $J=6.4\text{Hz}$, CH_3CHOH), 7.43 (brs, imidazole-H), 8.66 (brs, imidazole-H).

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EXAMPLE 7Step A:

p-Nitrobenzyl (5R,6S)-6-[1(R)-hydroxyethyl]-2-(3-pyridazinylmethylthio)carbapen-2-em 3-carboxylate

A solution of p-nitrobenzyl (5R,6S)-2-(diphenylphosphono)oxy-6-[1(R)-hydroxyethyl]carbapen-2-em 3-carboxylate (540 mg, 0.93 mmol) in anhydrous acetonitrile (5 cc) was cooled in an ice-bath under a nitrogen atmosphere and was treated with N,N-diisopropylethylamine (162 μ l, 0.93 mmol) followed by the dropwise addition of 3-mercaptomethylpyridazine* (117 mg, 0.93 mmol). A solid rapidly precipitated and after 30 minutes the suspension was diluted with ethyl acetate and was filtered giving the title compound (308 mg) as a white solid. The mother

* 3-Mercaptomethylpyridazine

K. Yu. Novitsuii, N. K. Sadovaya, E. F. Kas'yanova, L. K. Semna, Khimiya Geterotsiklicheskih Soedinenii Vol 6, No. 3, pp 412-414 (1970).

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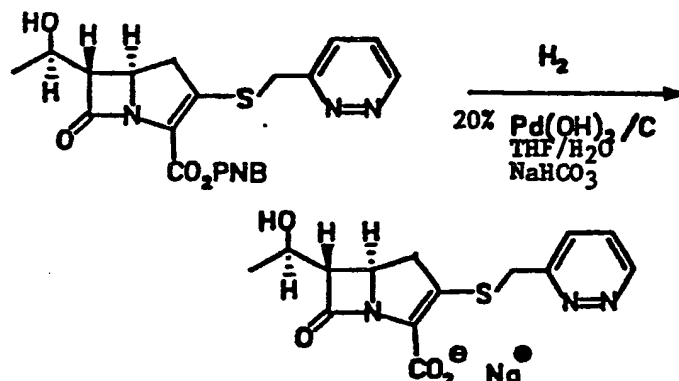
liquors were washed with 0.1N pH 7 phosphate buffer, dried over magnesium sulfate, filtered and evaporated under vacuum. The residue was chromatographed on a 1 mm x 20 cm x 20 cm silica gel GF plate, using 5% ethanol-methylene chloride as a developing solvent, to give additional product (28 mg) as a white solid. mp 156°C (dec) Thomas Hoover Capillary Melting Point Apparatus (uncorrected)

IR (Nujol) β -lactam \checkmark max 1740 cm^{-1}

NMR (CDCl_3) δ 1.31 (d, $J=6.1$ Hz, CH_3CHOH), 3.09 (dd, $J=8.9, 18.1$ Hz, CH_aH_b), 3.17 (dd, $J=2.8, 6.5$ Hz, H6), 3.61 (dd, $J=9.8, 18.1$ Hz, CH_aH_b), 4.20 (m, H5), 4.20 (m, CH_3CHOH), 4.28+4.31 (ABq, $J=14.8$ Hz, S- CH_2), 5.21+5.48 (ABq, $J=14.0$ Hz, CH_2Ar), 7.52 (dd, $J=5.0, 8.0$ Hz, pyridazinyl H5), 7.63 (d, $J=8.8$ Hz, 2ArH), 7.64 (d, $J=8.4$ Hz, pyridazinyl H4), 8.22 (d, $J=8.8$ Hz, 2ArH), 9.13 (d, $J=5.0$ Hz, pyridazinyl H6).

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STEP B:

Sodium (5R,6S)-6-[1(R)-hydroxyethyl]-2-(3-pyridazinylmethylthio)carbapen-2-em carboxylate

A suspension of p-nitrobenzyl (5R,6S)-6-[1(R)-hydroxyethyl]-2-(3-pyridazinylmethylthio)carbapen-2-em 3-carboxylate (5.5 g, 0.012 mol) in a mixture of water (0.75 L), containing sodium bicarbonate (1.01 g, 0.012 mol), and tetrahydrofuran (0.75 L), was hydrogenated for 2 hours at 40 psig in the presence of 20% Pd(OH)₂/C (1 g). The mixture was filtered through Solka-Floc and the solution was washed with ethyl ether. The aqueous phase concentrated under vacuum to ca. 500 cc and was freeze-dried giving (3.80 g) of a yellow solid. Crystallization from methanol gave the title compound (3.57 g) as an off-white solid.

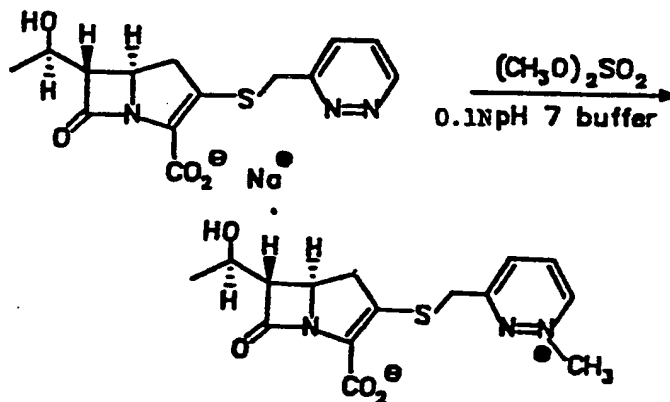
IR (Nujol) β -lactam \rightarrow max 1740 cm⁻¹

UV (H₂O) λ max 299 (ϵ 8,870) 93% H₂NOH
extinguished

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NMR (D_2O) δ 1.26 (d, $J=6.5$ Hz, CH_3CHOH), 2.99 (dd, $J=8.8, 17.8$ Hz, CH_aH_b), 3.23 (dd, $J=9.8, 17.6$ Hz, CH_aH_b), 3.36 (dd, $J=2.8, 5.9$ Hz, H6), 4.14 (m, CH_3CHOH), 4.14 (m, H5), 4.28+4.42 (ABq, $J=14.8$ Hz, S- CH_2), 7.83 (dd, $J=4.8, 8.4$ Hz, pyridazinyl H5), 7.99 (d, $J=8.6$ Hz, pyridazinyl H4), 9.12 (d, $J=4.8$ Hz, pyridazinyl H6).

STEP C:

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5R,6S-(1(R)-Hydroxyethyl)-2-(1-methyl-3-pyridazinium-methylthio)carbapen-2-em 3-carboxylate

A solution of sodium (5R,6S)-6-[1(R)-hydroxyethyl]-2-(3-pyridazinylmethylthio)carbapen-2-em 3-carboxylate (1.0 g, 0.0029 mol) in 0.1N pH 7 phosphate buffer (20 cc) was cooled in an ice-bath and treated with dimethylsulfate (2.2 ml, 0.023 mol). The mixture was stirred rapidly in the cold for 120 minutes, while incremental amounts of 1N NaOH were added in order to maintain a pH range of 6.8 to 7.2. The suspension was washed with ethylether and was loaded on a column of Dowex 50W-X4 resin (sodium form, 200-400 mesh, 2.5 cm x 37 cm). The ice-cooled jacketed column was eluted with de-ionized water and 25 cc fractions were collected. Fractions 23-63 were combined, concentrated under vacuum to 80 cc and lyophilized to give 0.55 g of a yellow solid. This material was crystallized from ethanol-water to give the title compound (0.47 g) as fine yellow needles.

IR (Nujol) β -lactam ν max 1750 cm^{-1}

UV (H_2O) λ max 293 (ϵ 8,610) 89% H_2NOH extinguished

NMR (D_2O) δ 1.27 (d, $J=6.5\text{ Hz}$, CH_3CHOH), 3.10 (dd, $J=8.5, 17.5\text{ Hz}$, $\text{CH}_2\text{H}_\text{b}$), 3.30 (dd, $J=9.8, 17.7\text{ Hz}$, $\text{CH}_2\text{H}_\text{a}$), 3.43 (dd, $J=2.8, 5.9\text{ Hz}$, H6), 4.21 (m, CH_3CHOH), 4.21 (m, H5), 4.38+4.50 (ABq, $J=15.7\text{ Hz}$, S- CH_2), 4.64 (s, N- CH_3), 8.51 (dd, $J=5.4, 8.2\text{ Hz}$, pyridazinyl H5), 8.60 (d, $J=8.0\text{ Hz}$, pyridazinyl H4), 9.58 (d, $J=5.5\text{ Hz}$, pyridazinyl H6).

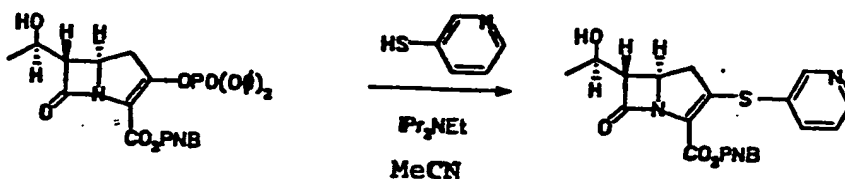
Anal. Calc'd for $\text{C}_{15}\text{H}_{17}\text{N}_3\text{O}_4\text{S} \cdot 2-1/2\text{H}_2\text{O}$:

C, 47.36; H, 5.83; N, 11.04

Found: C, 47.32; H, 5.77; N, 10.77.

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EXAMPLE 8STEP A:

p-Nitrobenzyl (5R,6S)-6-[(1R)-hydroxyethyl]-2-(3-pyridylthio)-carbapen-2-em-3-carboxylate

A solution of p-nitrobenzyl (5R,6S)-2-(diphenylphosphono)oxy 6-[(1R)-hydroxyethyl]carbapen-2-em-3-carboxylate (434 mg, 0.75 mmol) in anhydrous acetonitrile (2 ml) was cooled to ca. -20°C under a nitrogen atmosphere and treated dropwise over 5 minutes with a solution of 3-mercaptopyridine (108 mg, 0.97 mmol) in acetonitrile (1 ml) followed by N,N-diisopropylethylamine (0.169 ml, 0.97 mmol). After stirring in the cold for 30 minutes, the mixture was diluted with ethyl acetate, washed with water and brine, dried over magnesium sulfate, filtered, and evaporated under vacuum to give a pale yellow foam (343 mg). This material was dissolved in a small volume of ethyl acetate and the solution was diluted with ethyl ether and scratched to give the title compound (84 mg) as an off-white solid. The mother liquors were concentrated and chromatographed on three 1 mm x 20 x 20 cm silica gel GF plates using ethyl acetate as developing solvent to give additional product (113 mg) as a foam. This material was crystallized from ethyl acetate-ethyl ether to give the title compound (88 mg, 52% total yield) as fine white needles.

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mp 138-139.5°C (microhot stage);

IR (Nujol) ν_{\max} 3540, 1765, 1705, 1520, 1350 cm^{-1} ;

UV (dioxane) λ_{\max} 267 nm (ϵ 13,380), 319 nm (ϵ 15,050);

NMR (CDCl_3) δ 1.31 (d, $J=6.2$ Hz, CH_3CHOH), 2.69 (m, CH_2), 3.14 (dd, $J=2.8$ and 6.6 Hz, H6), 4.15 (dt, $J=2.8$ and 9.1 Hz, H5), 4.21 (dq, $J=6.5$ Hz, CH_3CHOH), 5.31 and 5.56 (two d, $J=13.7$ Hz, CH_2Ar), 7.36 (dd, $J=4.8$ and 8.0 Hz, pyridyl H5), 7.69 (d, $J=8.8$ Hz, 2ArH), 7.90 (ddd, $J=1.4$, 1.8 and 8.0 Hz, pyridyl H4), 8.25 (d, $J=8.8$ Hz, 2ArH), 8.69 (dd, $J=1.4$ and 4.8 Hz, pyridyl H6), 8.79 (d, $J=1.8$ Hz, pyridyl H2).

Anal. Calc'd for $\text{C}_{21}\text{H}_{19}\text{N}_3\text{O}_6\text{S}$:

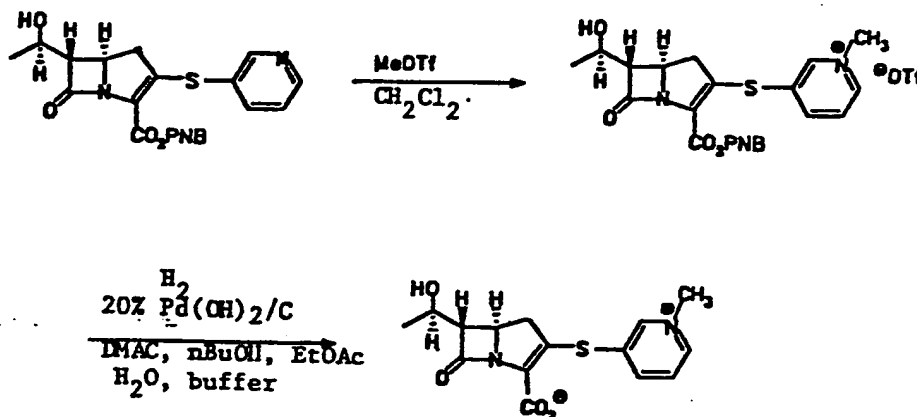
C, 57.14; H, 4.34; N, 9.52; S, 7.26

Found: C, 56.65; H, 4.35; N, 9.34; S, 7.63.

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STEP B:



(5R,6S)-6-[1(R)-Hydroxyethyl]-2-[(1-methyl-3-pyridinium)thio]carbapen-2-em-3-carboxylate

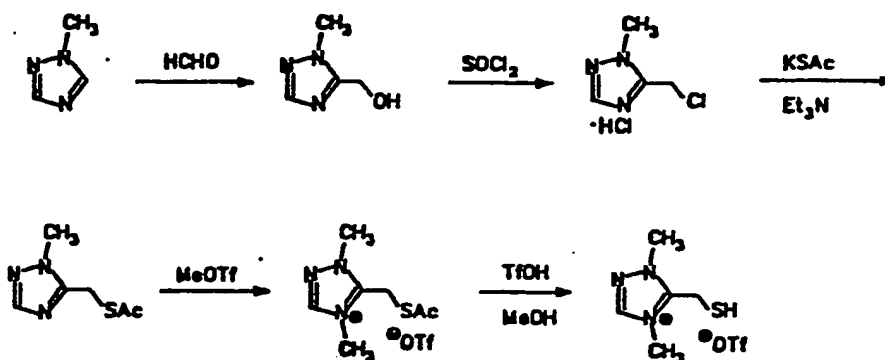
A solution of p-nitrobenzyl (5R,6S)-6-[1(R)-hydroxyethyl]-2-(3-pyridylthio)carbapen-2-em-3-carboxylate (110.4 mg, 0.25 mmol) in anhydrous methylene chloride (2.5 ml) was cooled in an ice bath under a nitrogen atmosphere and treated with methyl trifluoromethanesulfonate (31 μ l, 0.274 mmol). The mixture was stirred in the cold for 60 minutes. The solvent was decanted from the oily precipitate which

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- was washed with methylene chloride and dried under vacuum. The gummy residue was taken up in N,N-dimethylacetamide (2 ml), n-butanol (10 ml), ethyl acetate (5 ml), water (10 ml), and 0.5M pH 6.8
- 5 N-methylmorpholine-hydrochloric acid buffer (5 ml), treated with 20% palladium hydroxide on carbon (50 mg), and hydrogenated at 45 psi for 75 minutes. The mixture was filtered through celite to remove the catalyst which was washed with more water. The
- 10 aqueous portion of the filtrate was washed with methylene chloride and ether, concentrated under vacuum to ca. 3 ml, and loaded onto a column of Dowex 50W-X4 resin (sodium form, 200-400 mesh, 1.5 x 30 cm). The column was eluted with water in a cold
- 15 room; 170 drop fractions were collected. Fractions 15-25 were combined, concentrated under vacuum to 15 ml, filtered through a 0.45 μ filter, and lyophilized to give the title compound (47 mg) as a yellow, amorphous powder.
- 20 IR (Nujol) ν_{\max} 1755, 1594 cm^{-1} ;
 UV (0.05M pH 7.0 MOPS buffer) λ_{\max} 274 nm (ϵ 7,710), 296 nm (ϵ 8,240);
 UV (buffer + $\text{NH}_2\text{OH}\cdot\text{HCl}$) λ_{\max} 266 nm (ϵ 4,480), 316 nm (ϵ 1,780) and extinguished λ_{\max} 296 nm (ϵ ext. 6,790);
- 25 NMR (D_2O) δ 1.25 (d, $J=6.4$ Hz, CH_3CHOH), 2.80 (dd, $J=9.9$ and 17.5 Hz, CH_aH_b), 2.94 (dd, $J=8.5$ and 17.5 Hz, CH_aH_b), 3.45 (dd, $J=2.9$ and 5.9 Hz, H6), 4.23 (m, H5 and CH_3CHOH), 4.41
- 30 (s, NCH_3), 8.04 (dd, $J=6.0$ and 8.2 Hz, pyridyl H5), 8.63 (br d, $J=8.2$ Hz, pyridyl H4), 8.78 (br d, $J=6.0$ Hz, pyridyl H6), 9.01 (br s, pyridyl H2).

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EXAMPLE 9STEPS A - E

1,4-Dimethyl-5-mercaptomethyl-1,2,4-triazolium
trifluoromethanesulfonate

Step A. 5-Hydroxymethyl-1-methyl-1,2,4-triazole

A solution of 1-methyl-1,2,4-triazole (4.16 g, 0.05 mol) in formalin (20 ml) was heated overnight in a sealed tube at 135°C. After cooling, the solvent was evaporated under vacuum to give a clear liquid that partially solidified on standing. This material was distilled to give a white, crystalline solid (4.65 g) bp. ca. 110°C/0.25 mm. The solid product was recrystallized from ethyl acetate-hexane to afford the title compound (3.78 g, 67%) as white crystals.

IR (Nujol) ν_{max} 3180, 1505, 1290, 1200, 1045, 1000 cm^{-1} ;

NMR (CDCl_3) δ 3.95 (s, CH_3), 4.75 (d, $J=6.5$ Hz, CH_2), 5.49 (t, $J=6.5$ Hz, OH), 7.78 (s, H5);

Anal. Calc'd for $\text{C}_4\text{H}_7\text{N}_3\text{O}$:

C, 42.47; H, 6.24; N, 37.15

Found: C, 42.67; H, 6.16; N, 37.35.

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Step B. 5-Chloromethyl-1-methyl-1,2,4-triazole hydrochloride

The hydroxymethyl triazole from Step 1 (1.00 g) was added to ice-cold thionyl chloride (4 ml) and the resulting mixture was heated at reflux for 25 minutes. Excess thionyl chloride was evaporated under vacuum. The solid residue was recrystallized from ethanol-ethyl acetate to give the title compound (1.17 g, 79% yield) as white crystals.

IR (Nujol) ν_{max} 1585, 1400, 1265, 1250, 960 cm^{-1} ;

NMR (D_2O) δ 4.07 (s, CH_3), 4.85 (s, HOD), 5.04 (s, CH_2), 8.53 (s, H5);

Anal. Calc'd for $\text{C}_4\text{H}_7\text{Cl}_2\text{N}_3$:

C, 28.59; H, 4.20; N, 25.01

Found: C, 28.73; H, 4.16; N, 25.00.

Step C. 5-Acetylthiomethyl-1-methyl-1,2,4-triazole

A mixture of the chloromethyltriazole from Step 2 (609 mg, 3.63 mmol) and potassium thiolacetate (497 mg, 4.36 mmol) in anhydrous acetonitrile (7.3 ml) was treated with a speck of dicyclohexano-18-crown-6 and with triethylamine (531 μl , 3.81 mmol). The resulting mixture was stirred at room temperature for 3 hours. The mixture was filtered and the solids washed with acetonitrile. The filtrate and washings were evaporated under vacuum to a residue which was triturated with three portions of ethyl acetate. The ethyl acetate extracts were filtered, washed with brine, dried over magnesium sulfate, filtered, and evaporated under vacuum to afford the title compound (526 mg, 85%) as an orange liquid.

NMR (CDCl_3) δ 2.40 (s, CH_3CO), 3.91 (s, CH_3), 4.26 (s, CH_2), 7.80 (s, H5).

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Step D. 5-Acetylthiomethyl-1,4-dimethyl-1,2,4-triazolium trifluoromethanesulfonate

A solution of 3-acetylthiomethyl-2-methyl-1,2,4-triazole (244 mg, 1.43 mmol) in anhydrous methylene chloride (1.4 ml) was cooled in an ice bath under a nitrogen atmosphere and treated with methyl trifluoromethanesulfonate (194 μ l, 1.71 mmol). The resulting mixture was stirred in the cold for 30 minutes, then evaporated under vacuum. The residue was triturated three times with diethyl ether, then dissolved in anhydrous methylene chloride and evaporated under vacuum to afford the title compound (484 mg, 100%) as a viscous orange oil.

NMR (D_2O) δ 2.43 (s, CH_3CO), 3.95 (s, CH_3),
4.14 (s, CH_3), 4.62 (s, CH_2), 4.78 (s, HOD),
8.72 (s, H5).

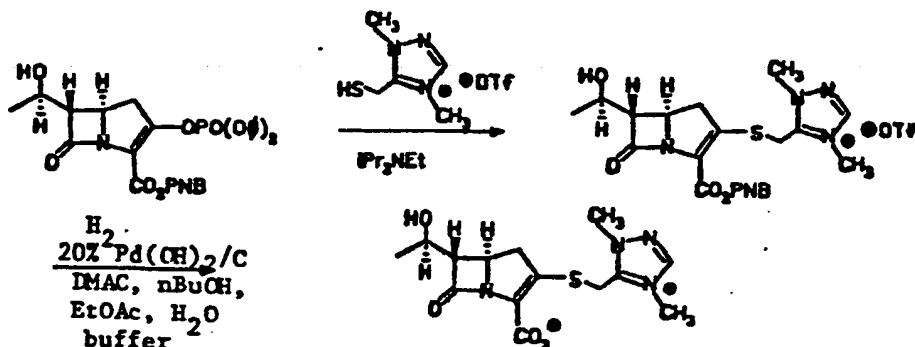
Step E. 1,4-Dimethyl-5-mercaptomethyl-1,2,4-triazolium trifluoromethanesulfonate

A solution of the product from the preceding step (484 mg, 1.43 mmol) in anhydrous methanol (1.4 ml) was treated with trifluoromethanesulfonic acid (127 μ l, 1.43 mmol) and kept at room temperature for 18.5 hours. The solution was diluted with ethyl ether to precipitate the product as an oil. The oil was washed four times with ethyl ether, diluted with anhydrous methylene chloride, and evaporated under vacuum to provide the title compound (344 mg, 82%) as a pale orange oil.

NMR (D_2O) δ 3.93 (s, CH_3), 4.08 (s, CH_3), 4.25
(s, CH_2), 4.78 (s, HOD), 8.72 (s, H5).

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STEP F:

(5R,6S)-2-(1,4-Dimethyl-1,2,4-triazol-5-ium)methylthio-6-[1(R)-hydroxyethyl]carbapen-2-em-3-carboxylate p-Nitrobenzyl (5R,6S)-2-(diphenylphosphono)-oxy-6-[1(R)-hydroxyethyl]carbapen-2-em-3-carboxylate (488 mg, 0.84 mmol) was added all at once to a solution of 1,4-dimethyl-5-mercaptopmethyl-1,2,4-triazolium trifluoromethanesulfonate (370 mg, 1.26 mmol) in anhydrous N,N-dimethylacetamide which was cooled to -20°C under a nitrogen atmosphere. The resulting solution was treated dropwise over 7.5 minutes with a solution of N,N-diisopropylethylamine (220 μl , 1.26 mmol) in dimethylacetamide (0.4 ml) and stirred an additional 30 minutes at -20°C . The reaction mixture was diluted with n-butanol (40 ml), ethyl acetate (20 ml), water (40 ml) and 0.5M pH 6.8 N-methylmorpholine-hydrochloric acid buffer (20 ml), treated with 20% palladium hydroxide on carbon (250 mg), and hydrogenated at 45 psi for 90 minutes. The mixture was filtered through a celite pad to remove the catalyst which was washed with water. The aqueous portion of the filtrate was washed with methylene chloride (3x) and ethyl ether, concentrated under vacuum to ca. 20 ml, and loaded onto a column of Dowex 50W-X4 resin (sodium form, 200-400 mesh, 200 ml). The column was eluted with water in a cold

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- room; 400 drop fractions were collected every 4.6 minutes. Fractions 13-18 were concentrated under vacuum to 22 ml, filtered through a 0.45 μ CR acrodisc, and lyophilized to afford the title
- 5 compound (121 mg) as a white amorphous solid.
IR (Nujol) ν_{\max} 3320 (br), 1760, 1595, 1565, 1240 cm^{-1} ;
UV (0.05M pH 7.0 MOPS buffer) λ_{\max} 294 nm (98% NH_2OH extinguished, $\epsilon_{\text{ext.}}$ 6,770);
- 10 NMR (D_2O) δ 1.29 (d, $J=6.4$ Hz, CH_3CHOH), 3.17 (dd, $J=8.6$ and 17.4 Hz, CH_aH_b), 3.32 (dd, $J=9.8$ and 17.4 Hz, CH_aH_b), 3.50 (dd, $J=2.9$ and 5.9 Hz, H6), 3.96 (s, NCH_3), 4.12 (s, NCH_3), 4.25 (m, H5 and CH_3CHOH), 4.80 (s, HOD), 8.77 (s, triazolium H).
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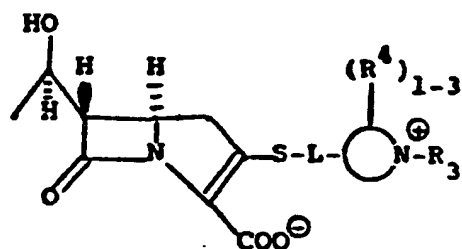
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EXAMPLE 10

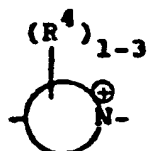
Utilizing the procedures of Examples 1-9
the following compounds are prepared:

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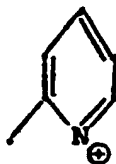
R³

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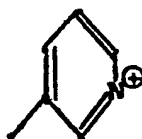
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CH₂CH₃

3 "

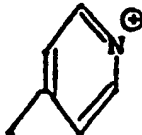
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4 "

"

CH₂CH₃

5 "

CH₂CH₂CH₃

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6 -CH₂-

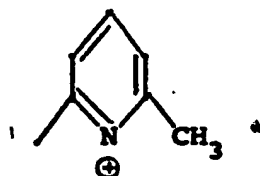
CH₂CH₃

7

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CH₃

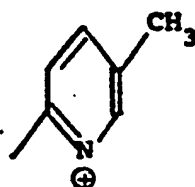
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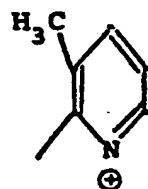
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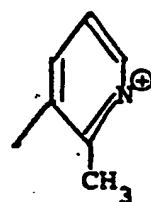
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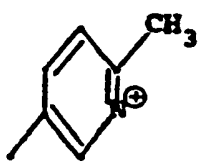
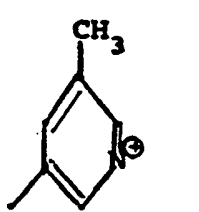
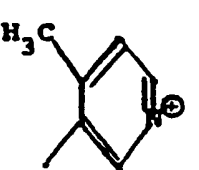
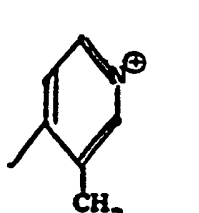
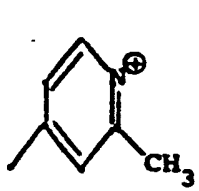
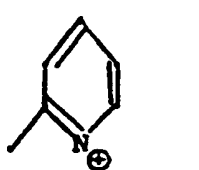
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| 10 | | | |
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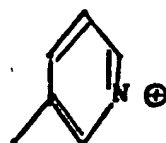
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18 -CH₂CH₂-



CH₃

5

19 "



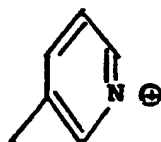
10

20 -CH-
CH₃



15

21 "



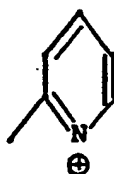
20

22 "



25

23 -CH₂-



CH₂

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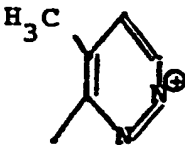
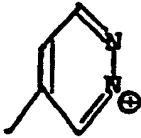
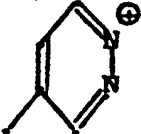
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16330IK

| | | | | |
|----|----|--------------------|---|-----------------|
| 5 | 24 | -CH ₂ - |  | OCH_2 |
| | 25 | " |  | " |
| 10 | | | | |
| | 26 | " |  | CH ₃ |
| 15 | | | | |
| | 27 | " |  | " |
| 20 | | | | |
| | 28 | " |  | " |
| 25 | | | | |
| | 29 | " |  | " |
| 30 | | | | |

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16330IK

30 -CH₂-

CH₃

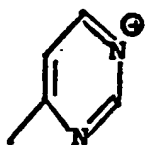
5



31 "

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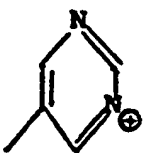
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32 "

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15



33 "

"

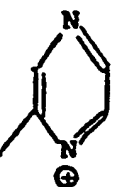
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34 "

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30 35 "

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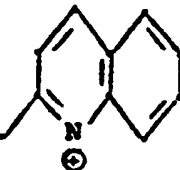

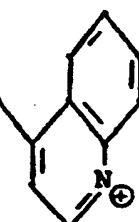

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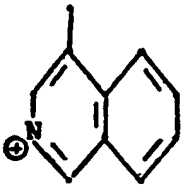

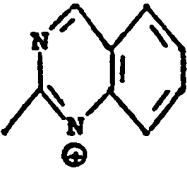
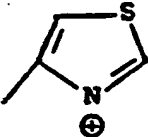
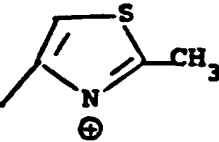
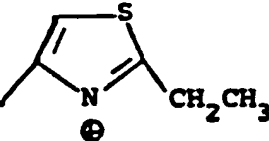
| | | | | |
|----|----|--------------------|---|-----------------|
| 5 | 36 | -CH ₂ - |  | CH ₃ |
| 10 | 37 | " |  | " |
| 15 | 38 | " |  | " |
| 20 | 39 | " |  | " |
| 25 | 40 | " |  | " |
| 30 | 41 | " |  | " |

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|----|----|--------------------|--|---|
| 5 | 42 | -CH ₂ - |  | CH ₃ |
| 10 | 43 | " |  | " |
| 15 | 44 | " |  | " |
| 20 | 45 | " |  | CH ₂ CH ₂ CH ₃ |
| 25 | 46 | " | " | CH ₂ CH ₃ |
| 30 | 47 | " |  | CH ₃ |
| | 48 | " |  | " |

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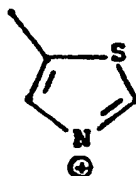
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49 -CH₂-

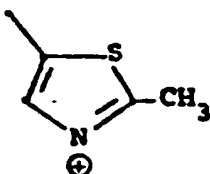
5



CH₃

50 "

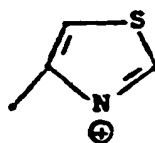
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51 -CH-
CH₃

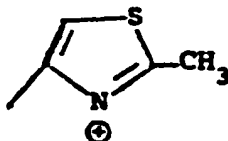
15



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52 "

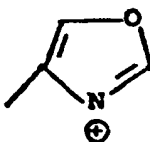
20



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53 -CH₂-

25



"

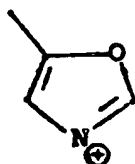
54 "

30

"

CH₂CH₃

55 "



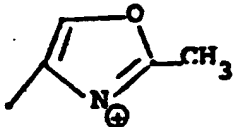
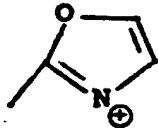
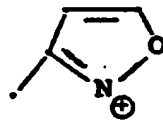
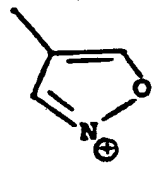
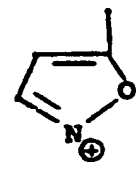
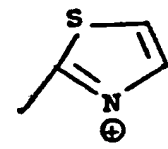
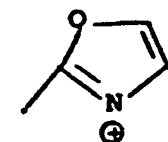
CH₃

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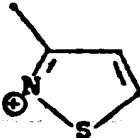
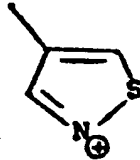
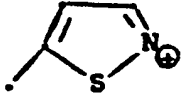
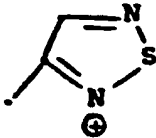
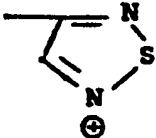
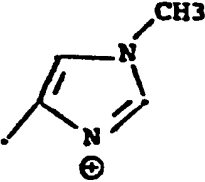
| | | | |
|----|------------------------------------|---|-----------------|
| 56 | -CH ₂ - |  | CH ₃ |
| 5 | 57 |  | " |
| 10 | 58 |  | " |
| 15 | 59 |  | " |
| 20 | 60 |  | " |
| 25 | 61 |  | " |
| 30 | 62 |  | " |
| | -CH ₂ CH ₂ - | | |

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| | | | | |
|----|----|--------------------|---|--|
| 5 | 63 | -CH ₂ - |  | CH ₃ |
| 10 | 64 | " |  | " |
| 15 | 65 | " |  | " |
| 20 | 66 | " |  | " |
| 25 | 67 | " |  | " |
| 30 | 68 | " |  | -CH ₂ CH ₂ CH ₃ |
| | 69 | " | " | -CH ₂ CH ₃ |

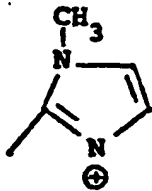
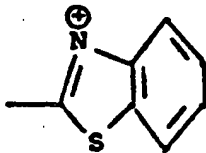
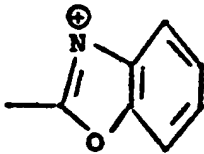
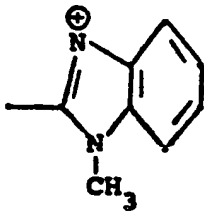

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16330IK

| | | | |
|----|-----------------------|---|---|
| 5 | 70 -CH ₂ - |  | -CH ₃ . |
| 10 | 71 " |  | " |
| 15 | 72 " |  | " |
| 20 | 73 " |  | " |
| 25 | 74 " |  | CH ₂ OCH ₃ |
| | 75 " | " | CH ₂ CN |
| 30 | 76 " | " | CH ₂ CO ₂ H |
| | 77 " | " | CH ₂ SO ₂ CH ₃ |

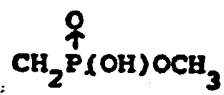
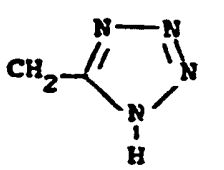

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16330IK

| | | | | |
|----|----|--------------------|---|---|
| | 78 | -CH ₂ - | " |  |
| 5 | 79 | " | " | CH ₂ SO ₃ H |
| | 80 | " | " | CH ₂ CONMe ₂ |
| | 81 | " | " | CH ₂ SOCH ₃ |
| 10 | 82 | " | " | CH ₂ NMe ₂ |
| 15 | 83 | " | " |  |
| 20 | 84 | " |  | CH ₂ OCH ₃ |
| | 85 | " | " | CH ₂ SCH ₃ |
| 25 | 86 | " | " | CH ₂ SOCH ₃ |
| | 87 | " | " | CH ₂ SO ₂ CH ₃ |
| 30 | 88 | " | " | CH ₂ CO ₂ H |
| | 89 | " | " | CH ₂ CONMe ₂ |


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16330IK

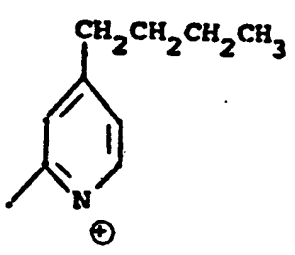
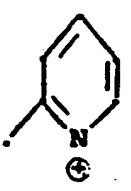
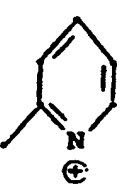
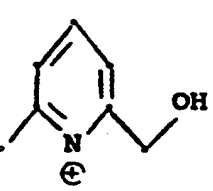
| | | | | |
|----|-----|--------------------|---|---|
| | 90 | -CH ₂ - | " | $\text{CH}_2\overset{\text{O}}{\underset{\uparrow}{\text{P}}}(\text{OH})\text{OCH}_3$ |
| 5 | 91 | " | " | $\text{CH}_2\text{SO}_3\text{H}$ |
| | 92 | " | " | CH_2CN |
| | 93 | " | " | CH_2NMe_2 |
| 10 | 94 | " | " | $\text{CH}_2\text{CH}_2\text{NMe}_2$ |
| 15 | 95 | " |  | CH_2OCH_3 |
| | 96 | " | " | CH_2NMe_2 |
| 20 | 97 | " | " | $\text{CH}_2\text{CH}_2\text{NMe}_2$ |
| | 98 | " | " | CH_2CN |
| | 99 | " | " | CH_2SCH_3 |
| 25 | 100 | " | " | CH_2SOCH_3 |
| | 101 | " | " | $\text{CH}_2\text{SO}_2\text{CH}_3$ |
| 30 | 102 | " | " | $\text{CH}_2\text{CO}_2\text{H}$ |
| | 103 | " | " | $\text{CH}_2\text{CONMe}_2$ |

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2361P/0840A

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16330IK

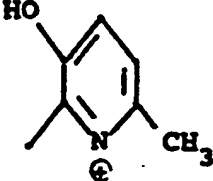
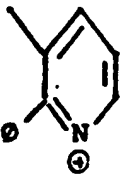

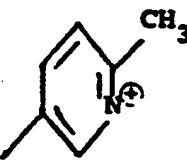
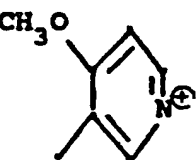
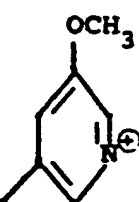
| | | | | |
|----|-----|--|---|---|
| 5 | 104 | -CH ₂ - | " | $\text{CH}_2\overset{\text{O}}{\underset{\text{P}}{\text{P}}}(\text{OH})\text{OCH}_3$ |
| | 105 | " | " | $\text{CH}_2\text{SO}_3\text{H}$ |
| 10 | 106 | " |  | CH_3 |
| 15 | 107 | -CH ₂ CH ₂ CH ₂ - |  | " |
| 20 | 108 | -CH ₂ CH- CH ₂ OH |  | " |
| 25 | 109 | -CH ₂ - |  | " |
| 30 | | | | |

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2361P/0840A

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16330IK

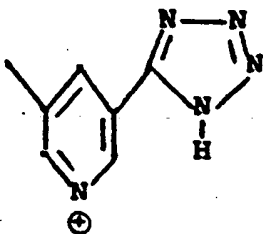
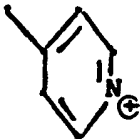
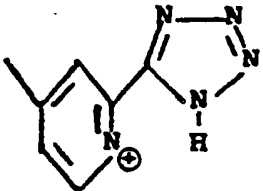



| | | | | |
|----|-----|--|---|-----------------|
| 5 | 110 | -CH ₂ - |  | CH ₃ |
| 10 | 111 | " |  | " |
| 15 | 112 | -CH ₂ CH ₂ CH ₂ - |  | " |
| 20 | 113 | -CH ₂ CH ₂ - |  | " |
| 25 | 114 | -CH ₂ - |  | " |
| 30 | 115 | " |  | " |

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16330IK

| | | | |
|----|--|---|---------------------------------|
| 5 | 116 -CH ₂ - |  | CH ₃ |
| 10 | 117 -CH ₂ CH ₂ CH ₂ - |  | . |
| 15 | 118 CH ₂ |  | . |
| 20 | 119 bond |  | . |
| 25 | 120 " |  | CH ₂ CH ₃ |
| 30 | 121 " |  | CH ₂ CH ₃ |

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2361P/0840A

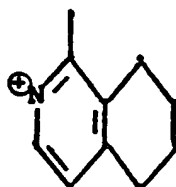
-89-

16330IK

122 bond

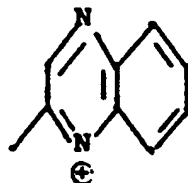
CH₃ .

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123 -CH₂-

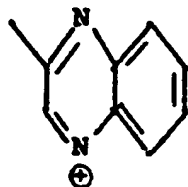
10

124 "



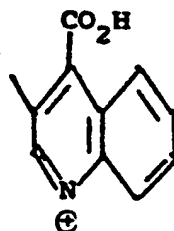
15

125 "



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25 126 "



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2360P/0840A

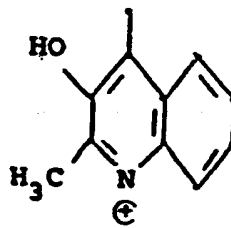
2361P/0840A

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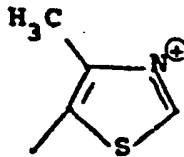
16330IK

127 -CH₂-

5

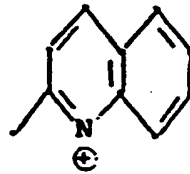
CH₃ .128 -CH₂CH₂-

10

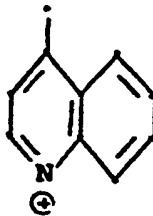


129 bond

15



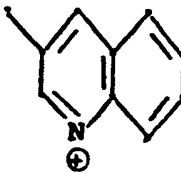
20 130 "



25

131 "

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2360P/0840A

2361P/0840A

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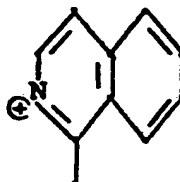
16330IK

132 bond

CH₃

5

133 "



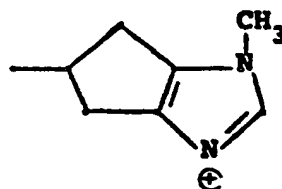
10

134 "

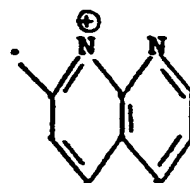


15

135 "



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136 -CH-
CH₃

25

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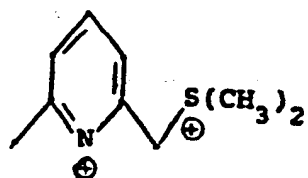
2360P/0840A

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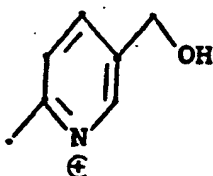
16330IK

137 -CH₂-
5

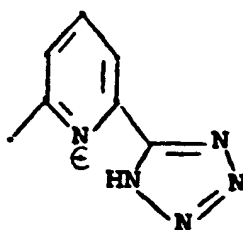


CH₃

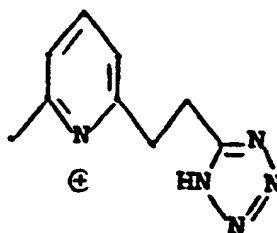
138 "
10



139 "
15

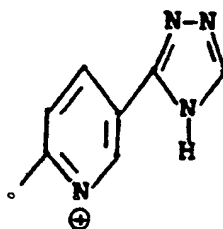


140 "
20



141 "
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141 "
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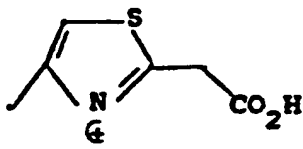
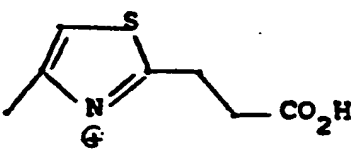
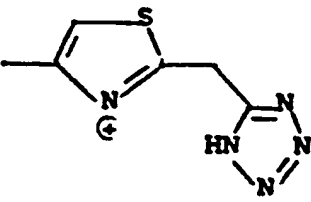
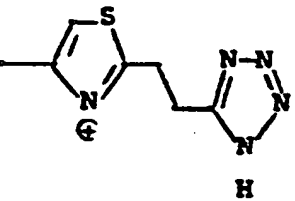
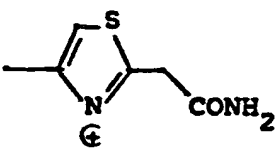
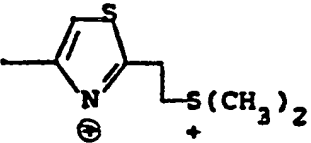


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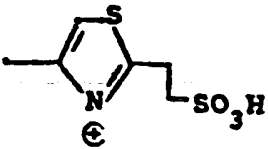
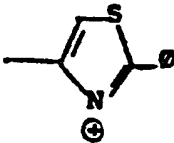
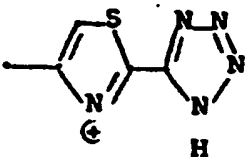
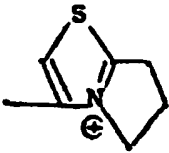
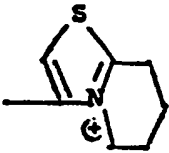
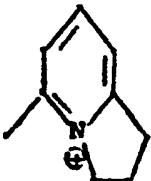
| | | | |
|-----|-----------------|--|-----------------|
| 142 | CH ₂ |  | CH ₃ |
| 5 | | | |
| 143 | " |  | " |
| 10 | | | |
| 144 | " |  | " |
| 15 | | | |
| 145 | " |  | " |
| 20 | | | |
| 146 | " |  | " |
| 25 | | | |
| 147 | " |  | " |
| 30 | | | |

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| | | | |
|----|------------------------|---|-----------------|
| 5 | 148 -CH ₂ - |  | CH ₃ |
| 10 | 149 " |  | " |
| 15 | 150 " |  | " |
| 20 | 151 " |  | -- |
| 25 | 152 " |  | -- |
| 30 | 153 " |  | -- |

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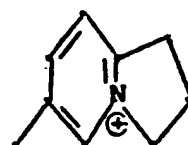
154 -CH₂-

5



155 "

10



156 "

15



157 "

20



158 $\begin{array}{c} \text{CH}_3 \\ | \\ -\text{CHCH}_2- \end{array}$

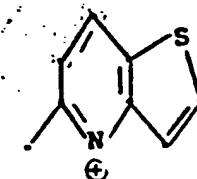
25



CH₃

159 -CH₂-

30

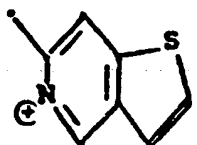
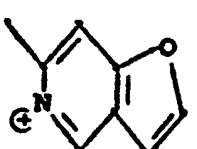
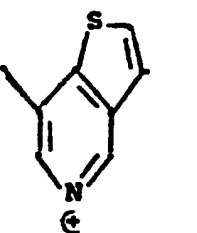
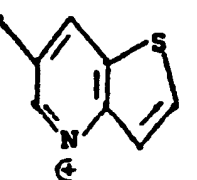
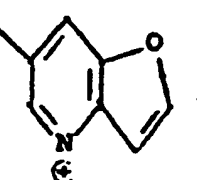
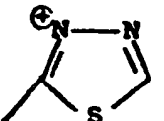


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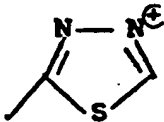
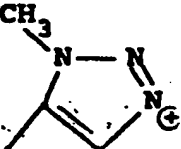
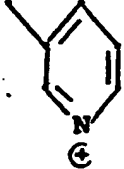
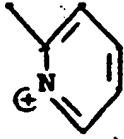

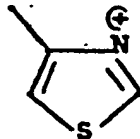
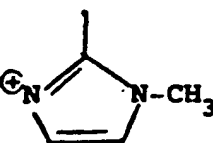
| | | | | |
|----|-----|--------------------|---|-----------------|
| 5 | 160 | -CH ₂ - |  | CH ₃ |
| 10 | 161 | " |  | " |
| 15 | 162 | " |  | " |
| 20 | 163 | " |  | " |
| 25 | 164 | " |  | " |
| 30 | 165 | " |  | " |

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| | | | |
|-----|--------------------|---|-----------------------------------|
| 166 | -CH ₂ - |  | CH ₃ |
| 5 | 167 | " | " |
| | |  | |
| 10 | 168 | " | CH ₂ CONH ₂ |
| | |  | |
| 15 | 169 | " | " |
| | |  | |
| 20 | 170 | " | " |
| | |  | |
| 25 | 171 | " | " |
| | |  | |
| 30 | 172 | bond | CH ₃ |
| | |  | |

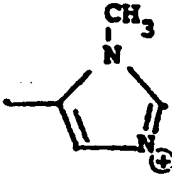
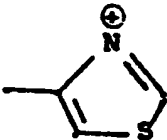
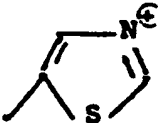
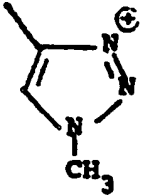
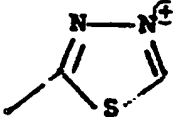
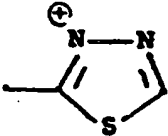
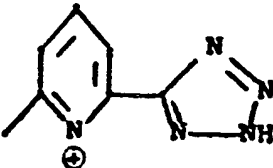
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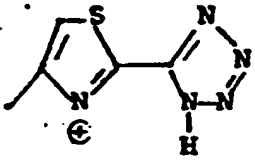
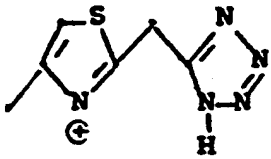
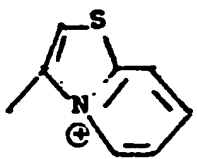
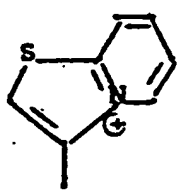
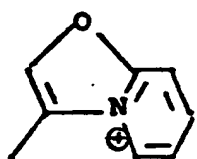
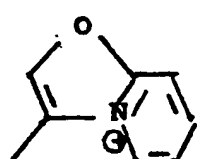
| | | | | |
|----|-----|------|--|-----------------|
| 5 | 173 | bond |  | CH ₃ |
| 10 | 174 | " |  | " |
| 15 | 175 | " |  | " |
| 20 | 176 | " |  | " |
| 25 | 177 | " |  | " |
| 30 | 178 | " |  | " |
| | 179 | " |  | " |

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| | | | |
|-----|--------------------|---|-----------------|
| 180 | -CH ₂ - |  | CH ₃ |
| 5 | | | |
| 181 | " |  | " |
| 10 | | | |
| 182 | " |  | -- |
| 15 | | | |
| 183 | bond |  | -- |
| 20 | | | |
| 184 | CH ₂ |  | -- |
| 25 | | | |
| 185 | bond |  | -- |
| 30 | | | |

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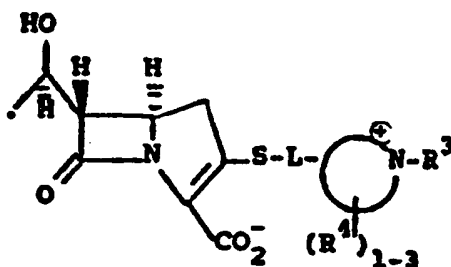
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EXAMPLE 11

Utilizing the procedures of Examples 1-9,
the following compounds are prepared:

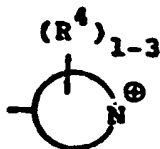
5



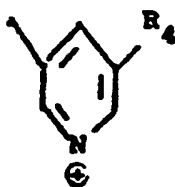
10

Com-
pound
No.

L

R₃R₄

15

1 CH₂CH₃CO₂H

20

2 "

"

" CONH₂

3 "

"

" CN

25

4 "

"

" OH

5 "

"

" SO₂NH₂

30

6 "

"

" SO₃H

7 "

"

" NMe₂

8 "

"

" CONMe₂

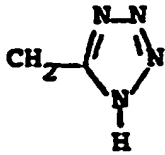
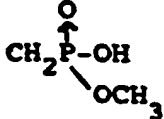
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| | | | | | |
|----|----|---|---|---|---|
| | 9 | " | " | " | CH_2NMe_2 |
| | 10 | " | " | " | CH_2CN |
| 5 | 11 | " | " | " | CH_2CONH_2 |
| | 12 | " | " | " | $\text{CH}_2\text{CO}_2\text{H}$ |
| | 13 | " | " | " | CH_2SCH_3 |
| 10 | 14 | " | " | " | CH_2SOCH_3 |
| | 15 | " | " | " | $\text{CH}_2\text{SO}_2\text{CH}_3$ |
| 15 | 16 | " | " | " | SO_2CH_3 |
| | 17 | " | " | " | SOCH_3 |
| 20 | 18 | " | " | " |  |
| | 19 | " | " | " | $\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$ |
| 25 | 20 | " | " | " | $\text{CH}_2\text{SO}_3\text{H}$ |
| | 21 | " | " | " | CH_2OCH_3 |
| 30 | 22 | " | " | " |  |


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16330IK

| | | | | | |
|----|----|---|--|---|---|
| | 23 | " | " | " | CH ₂ CH ₂ SO ₃ H |
| | 24 | " | " | " | CF ₃ |
| 5 | 25 | " | " | " | CH ₂ OC(=O)NH ₂ |
| | 26 | " | " | " | CH ₂ SO ₂ NH ₂ |
| 10 | 27 | " | " | " | Br |
| | 28 | " | " | " | Cl |
| | 29 | " | " | " | F |
| 15 | 30 | " | " | " | CO ₂ H |
| 20 | | |  | | |
| | 31 | " | " | " | CONH ₂ |
| 25 | 32 | " | " | " | CN |
| | 33 | " | " | " | OH |
| 30 | 34 | " | " | " | SONH ₂ |

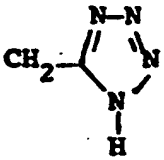
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| | | | | | |
|----|----|---|---|---|---|
| | 35 | " | " | " | SO ₃ H |
| | 36 | " | " | " | NMe ₂ |
| 5 | 37 | " | " | " | CONMe ₂ |
| | 38 | " | " | " | CH ₂ NMe ₂ |
| | 39 | " | " | " | CH ₂ CN |
| 10 | 40 | " | " | " | CH ₂ CONH ₂ |
| | 41 | " | " | " | CH ₂ CO ₂ H |
| 15 | 41 | " | " | " | CH ₂ SCH ₃ |
| | 43 | " | " | " | CH ₂ SOCH ₃ |
| | 44 | " | " | " | CH ₂ SO ₂ CH ₃ |
| 20 | 45 | " | " | " | SO ₂ CH ₃ |
| | 46 | " | " | " | SOCH ₃ |
| 25 | 47 | " | " | " |  |
| 30 | 48 | " | " | " | CH ₂ CH ₂ CO ₂ H |
| | 49 | " | " | " | CH ₂ SO ₃ H |
| | 50 | " | " | " | CH ₂ OCH ₃ |

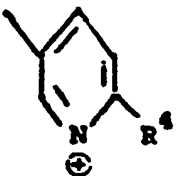
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| | | | | | |
|----|----|---|--|---|--|
| | 51 | " | " | " | $\text{CH}_2\text{P}(\text{O})(\text{OH})\text{OCH}_3$ |
| 5 | 52 | " | " | " | $\text{CH}_2\text{CH}_2\text{SO}_3\text{H}$ |
| | 53 | " | " | " | CF_3 |
| 10 | 54 | " | " | " | CH_2OCNH_2 |
| | 55 | " | " | " | $\text{CH}_2\text{SO}_2\text{NH}_2$ |
| 15 | 56 | " | " | " | $\text{CH}_2\text{SO}_2\text{NMe}_2$ |
| | 57 | " |  | " | CO_2H |
| 20 | 58 | " | " | " | CONH_2 |
| | 59 | " | " | " | CN |
| 25 | 60 | " | " | " | OCH_3 |
| | 61 | " | " | " | SO_2NH_2 |
| 30 | 62 | " | " | " | SO_3H |
| | 63 | " | " | " | NMe_2 |

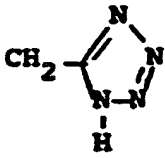
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| | | | | | |
|----|----|---|---|---|---|
| | 64 | " | " | " | CONMe ₂ |
| | 65 | " | " | " | CH ₂ NMe ₂ |
| 5 | 66 | " | " | " | CH ₂ CN |
| | 67 | " | " | " | CH ₂ CONH ₂ |
| | 68 | " | " | " | CH ₂ CO ₂ H |
| 10 | 69 | " | " | " | CH ₂ SCH ₃ |
| | 70 | " | " | " | CH ₂ SOCH ₃ |
| 15 | 71 | " | " | " | CH ₂ SO ₂ CH ₃ |
| | 72 | " | " | " | SO ₂ CH ₃ |
| | 73 | " | " | " | SOCH ₃ |
| 20 | 74 | " | " | " |  |
| 25 | 75 | " | " | " | CH ₂ CH ₂ CO ₂ H |
| | 76 | " | " | " | CH ₂ SO ₃ H |
| 30 | 77 | " | " | " | CH ₂ OCH ₃ |

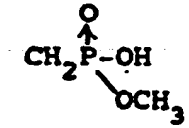
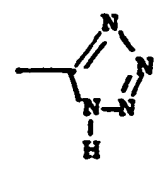
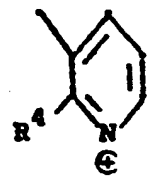
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| | | | | | |
|----|----|---|---|---|--|
| | 78 | " | " | " |  |
| 5 | 79 | " | " | " | $\text{CH}_2\text{CH}_2\text{SO}_3\text{H}$ |
| | 80 | " | " | " | CF_3 |
| 10 | 81 | " | " | " | $\text{CH}_2\text{OC(=O)NH}_2$ |
| | 82 | " | " | " | $\text{CH}_2\text{SO}_2\text{NH}_2$ |
| 15 | 83 | " | " | " | $\text{CH}_2\text{SO}_2\text{NMe}_2$ |
| | 84 | " | " | " |  |
| 20 | | | | | |
| | 85 | " |  | " | CO_2H |
| 25 | | | | | |
| | 86 | " | " | " | CONH_2 |
| 30 | 87 | " | " | " | CN |
| | 88 | " | " | " | OCH_3 |

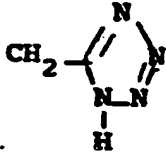
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| | | | | | |
|----|-----|-----------------|---|---|---|
| | 89 | " | " | " | SO ₂ NH ₂ |
| | 90 | " | " | " | SO ₃ H |
| 5 | 91 | " | " | " | NMe ₂ |
| | 92 | " | " | " | CONMe ₂ |
| | 93 | " | " | " | CH ₂ NMe ₂ |
| 10 | 94 | " | " | " | CH ₂ CN |
| | 95 | " | " | " | CH ₂ CONH ₂ |
| 15 | 96 | " | " | " | CH ₂ CO ₂ H |
| | 97 | " | " | " | CH ₂ SCH ₃ |
| | 98 | " | " | " | CH ₂ SOCH ₃ |
| 20 | 99 | CH ₃ | " | " | CH ₂ SO ₂ CH ₃ |
| | 100 | " | " | " | SO ₂ CH ₃ |
| 25 | 101 | " | " | " | SOCH ₃ |
| | 102 | " | " | " |  |
| 30 | 103 | " | " | " | CH ₂ CH ₂ CO ₂ H |

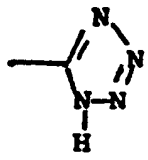
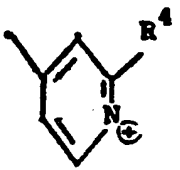
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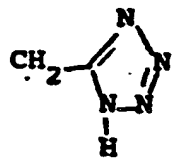
| | | | | | |
|----|-----|-----------------|---|---|---|
| | 104 | " | " | " | $\text{CH}_2\text{SO}_3\text{H}$ |
| | 105 | " | " | " | CH_2OCH_3 |
| 5 | 106 | " | " | " | $\text{CH}_2\text{P}(\text{OH})(\text{OCH}_3)$ |
| | 107 | " | " | " | $\text{CH}_2\text{CH}_2\text{SO}_3\text{H}$ |
| 10 | 108 | " | " | " | CF_3 |
| | 109 | " | " | " | CH_2OCNH_2 |
| 15 | 110 | " | " | " | $\text{CH}_2\text{SO}_2\text{NH}_2$ |
| | 111 | " | " | " | $\text{CH}_2\text{SO}_2\text{NMe}_2$ |
| 20 | 112 | " | " | " |  |
| 25 | 113 | $-\text{CH}_2-$ |  | " | CO_2H |
| 30 | 114 | " | " | " | CONH_2 |
| | 115 | " | " | " | CN |

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| | | | | | |
|----|-----|---|---|---|---|
| | 116 | " | " | " | OCH ₃ |
| | 117 | " | " | " | SO ₂ NH ₂ |
| 5 | 118 | " | " | " | SO ₃ H |
| | 119 | " | " | " | NMe ₂ |
| | 120 | " | " | " | CONMe ₂ |
| 10 | 121 | " | " | " | CH ₂ NMe ₂ |
| | 122 | " | " | " | CH ₂ CN |
| 15 | 123 | " | " | " | CH ₂ CONH ₂ |
| | 124 | " | " | " | CH ₂ CO ₂ H |
| | 125 | " | " | " | CH ₂ SCH ₃ |
| 20 | 126 | " | " | " | CH ₂ SOCH ₃ |
| | 127 | " | " | " | CH ₂ SO ₂ CH ₃ |
| 25 | 128 | " | " | " | SO ₂ CH ₃ |
| | 129 | " | " | " | SOCH ₃ |
| 30 | 130 | " | " | " |  |

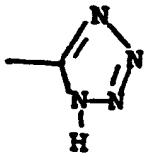
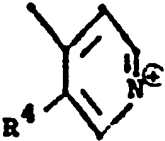
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| | | | | | |
|----|-----|---|---|---|--|
| | 131 | " | " | " | CH ₂ CH ₂ CO ₂ H |
| | 132 | " | " | " | CH ₂ SO ₃ H |
| 5 | 133 | " | " | " | CH ₂ OCH ₃ |
| | 134 | " | " | " | $\begin{array}{c} \text{O} \\ \uparrow \\ \text{CH}_2\text{P}-\text{OH} \\ \quad \quad \quad \backslash \\ \quad \quad \quad \text{OCH}_3 \end{array}$ |
| 10 | 135 | " | " | " | CH ₂ CH ₂ SO ₃ H |
| | 136 | " | " | " | CF ₃ |
| 15 | 137 | " | " | " | $\begin{array}{c} \text{O} \\ \parallel \\ \text{CH}_2\text{OCNH}_2 \end{array}$ |
| | 138 | " | " | " | CH ₂ SO ₂ NH ₂ |
| 20 | 139 | " | " | " | CH ₂ SO ₂ NMe ₂ |
| 25 | 140 | " | " | " |  |
| 30 | 141 | " |  | " | CO ₂ H |
| | 142 | " | " | " | CONH ₂ |

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| | | | | | |
|----|-----|---|---|---|---|
| | 143 | " | " | " | CN |
| | 144 | " | " | " | OH |
| 5 | 145 | " | " | " | OCH ₃ |
| | 146 | " | " | " | SO ₂ NH ₂ |
| | 147 | " | " | " | SO ₃ H |
| 10 | 148 | " | " | " | NMe ₂ |
| | 149 | " | " | " | CONMe ₂ |
| 15 | 150 | " | " | " | CH ₂ NMe ₂ |
| | 151 | " | " | " | CH ₂ CN |
| | 152 | " | " | " | CH ₂ CONH ₂ |
| 20 | 153 | " | " | " | CH ₂ CO ₂ H |
| | 154 | " | " | " | CH ₂ SCH ₃ |
| 25 | 155 | " | " | " | CH ₂ SOCH ₃ |
| | 156 | " | " | " | CH ₂ SO ₂ CH ₃ |
| | 157 | " | " | " | SO ₂ CH ₃ |
| 30 | 158 | " | " | " | SOCH ₃ |

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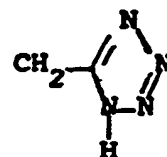
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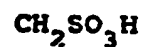
5 159 " "



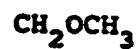
160 " "



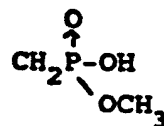
161 " "



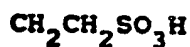
10 162 " "



163 " "



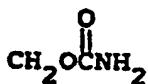
15 164 " "



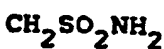
165 " "



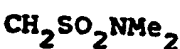
20 166 " "



167 " "



25 168 " "



30 169 " "




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| | | | | | |
|----|-----|---|---|---|-----------------------------------|
| | 170 | " | " | " | F |
| | 171 | " | " | " | Cl |
| 5 | 172 | " | " | " | Br |
| 10 | 173 | " |  | " | CO ₂ H |
| | 174 | " | " | " | CONH ₂ |
| 15 | 175 | " | " | " | CN |
| | 176 | " | " | " | SO ₂ NH ₂ |
| 20 | 177 | " | " | " | SO ₃ H |
| | 178 | " | " | " | NMe ₂ |
| | 179 | " | " | " | CONMe ₂ |
| 25 | 180 | " | " | " | CH ₂ NMe ₂ |
| | 181 | " | " | " | CH ₂ CN |
| 30 | 182 | " | " | " | CH ₂ CONH ₂ |
| | 183 | " | " | " | CH ₂ CO ₂ H |

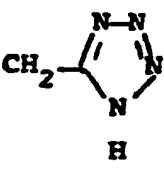
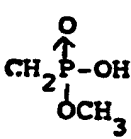

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| | | | | | |
|----|-----|---|---|---|---|
| | 184 | " | " | " | CH_2SCH_3 |
| | 185 | " | " | " | CH_2SOCH_3 |
| 5 | 186 | " | " | " | $\text{CH}_2\text{SO}_2\text{CH}_3$ |
| | 187 | " | " | " | SO_2CH_3 |
| 10 | 188 | " | " | " |  |
| | 189 | " | " | " | $\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$ |
| 15 | 190 | " | " | " | $\text{CH}_2\text{SO}_3\text{H}$ |
| | 191 | " | " | " | CH_2OCH_3 |
| 20 | 192 | " | " | " |  |
| | 193 | " | " | " | $\text{CH}_2\text{CH}_2\text{SO}_3\text{H}$ |
| 25 | 194 | " | " | " | CF_3 |
| | 195 | " | " | " |  |
| 30 | 196 | " | " | " | $\text{CH}_2\text{SO}_2\text{NH}_2$ |

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| | | | | | |
|----|-----|---|---|---|-----------------------------------|
| 5 | 197 | " | " | " | CO ₂ H |
| | | | | | |
| | 198 | " | " | " | CONH ₂ |
| 10 | 199 | " | " | " | CN |
| | 200 | " | " | " | OH |
| | 201 | " | " | " | SO ₂ NH ₂ |
| 15 | 202 | " | " | " | SO ₃ H |
| | 203 | " | " | " | NMe ₂ |
| 20 | 204 | " | " | " | CONMe ₂ |
| | 205 | " | " | " | CH ₂ NMe ₂ |
| | 206 | " | " | " | CH ₂ CN |
| 25 | 207 | " | " | " | CH ₂ CONH ₂ |
| | 208 | " | " | " | CH ₂ CO ₂ H |
| 30 | 209 | " | " | " | CH ₂ SCH ₃ |
| | 210 | " | " | " | CH ₂ SOCH ₃ |



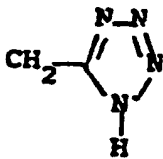
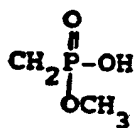

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| | | | | | |
|----|-----|---|---|---|---|
| | 211 | " | " | " | $\text{CH}_2\text{SO}_2\text{CH}_3$ |
| | 212 | " | " | " | SO_2CH_3 |
| 5 | 213 | " | " | " | SOCH_3 |
| 10 | 214 | " | " | " |  |
| | 215 | " | " | " | $\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$ |
| 15 | 216 | " | " | " | $\text{CH}_2\text{SO}_3\text{H}$ |
| | 217 | " | " | " | CH_2OCH_3 |
| 20 | 218 | " | " | " |  |
| | 219 | " | " | " | $\text{CH}_2\text{CH}_2\text{SO}_3\text{H}$ |
| 25 | 220 | " | " | " | CF_3 |
| | 221 | " | " | " |  |
| 30 | 222 | " | " | " | $\text{CH}_2\text{SO}_2\text{NH}_2$ |
| | 223 | " | " | " | Br |

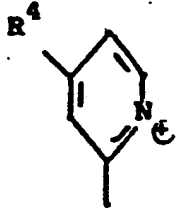
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| | | | | | |
|----|-----|---|---|---|-----------------------------------|
| | 224 | " | " | " | Cl |
| | 225 | " | " | " | F |
| 5 | 226 | " |  | " | CO ₂ H |
| 10 | 227 | " | " | " | CONH ₂ |
| | 228 | " | " | " | CN |
| 15 | 229 | " | " | " | SO ₂ NH ₂ |
| | 230 | " | " | " | SO ₃ H |
| 20 | 231 | " | " | " | NMe ₂ |
| | 232 | " | " | " | CONMe ₂ |
| | 233 | " | " | " | CH ₂ NMe ₂ |
| 25 | 234 | " | " | " | CH ₂ CN |
| | 235 | " | " | " | CH ₂ CONH ₂ |
| | 236 | " | " | " | CH ₂ CO ₂ H |
| 30 | 237 | " | " | " | CH ₂ SCH ₃ |

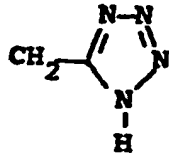
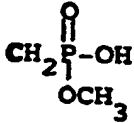
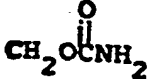
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| | | | | | |
|----|-----|---|---|---|---|
| | 238 | • | • | • | CH_2SOCH_3 |
| | 239 | • | • | • | $\text{CH}_2\text{SO}_2\text{CH}_3$ |
| 5 | 240 | • | • | • | SO_2CH_3 |
| | 241 | • | • | • | SOCH_3 |
| 10 | 242 | • | • | • |  |
| | 243 | • | • | • | $\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$ |
| 15 | 244 | • | • | • | $\text{CH}_2\text{SO}_3\text{H}$ |
| | 245 | • | • | • | CH_2OCH_3 |
| 20 | 246 | • | • | • |  |
| | 247 | • | • | • | $\text{CH}_2\text{CH}_2\text{SO}_3\text{H}$ |
| 25 | 248 | • | • | • | CF_3 |
| | 249 | • | • | • |  |
| 30 | 250 | • | • | • | $\text{CH}_2\text{SO}_2\text{NH}_2$ |

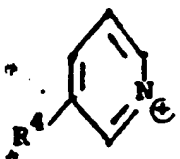
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| | | | | | |
|----|-----|---|---|---|-----------------------------------|
| 5 | 251 | " |  | " | CO ₂ H |
| | 252 | " | " | " | CONH ₂ |
| | 253 | " | " | " | CN |
| | 254 | " | " | " | OH |
| | 255 | " | " | " | SO ₂ NH ₂ |
| 10 | 256 | " | " | " | SO ₃ H |
| | 257 | " | " | " | NMe ₂ |
| | 258 | " | " | " | CONMe ₂ |
| | 259 | " | " | " | CH ₂ NMe ₂ |
| | 260 | " | " | " | CH ₂ CN |
| 20 | 261 | " | " | " | CH ₂ CONH ₂ |
| | 262 | " | " | " | CH ₂ CO ₂ H |
| | 263 | " | " | " | CH ₂ SCH ₃ |
| | 264 | " | " | " | CH ₂ SOCH ₃ |
| | | " | " | " | |
| 30 | | " | " | " | |
| | | " | " | " | |
| | | " | " | " | |
| | | " | " | " | |
| | | " | " | " | |

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| | | | | | |
|----|-----|---|---|---|--|
| | 265 | • | • | • | $\text{CH}_2\text{SO}_2\text{CH}_3$ |
| | 266 | • | • | • | SO_2CH_3 |
| 5 | 267 | • | • | • | SOCH_3 |
| 10 | 268 | • | • | • | $ \begin{array}{c} \text{N}-\text{N} \\ \diagup \quad \diagdown \\ \text{CH}_2-\text{C} \quad \text{N} \\ \diagdown \quad \diagup \\ \text{N} \\ \\ \text{H} \end{array} $ |
| | 269 | • | • | • | $\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$ |
| 15 | 270 | • | • | • | $\text{CH}_2\text{SO}_3\text{H}$ |
| | 271 | • | • | • | CH_2OCH_3 |
| 20 | 272 | • | • | • | $ \begin{array}{c} \text{O} \\ \\ \text{CH}_2-\text{P}-\text{OH} \\ \\ \text{OCH}_3 \end{array} $ |
| | 273 | • | • | • | $\text{CH}_2\text{CH}_2\text{SO}_3\text{H}$ |
| 25 | 274 | • | • | • | CF_3 |
| | 275 | • | • | • | $ \begin{array}{c} \text{O} \\ \\ \text{CH}_2-\text{OCNH}_2 \end{array} $ |
| 30 | 276 | • | • | • | $\text{CH}_2\text{SO}_2\text{NH}_2$ |

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Br

277

278

5 279

Cl

F

10

15

20

25

30

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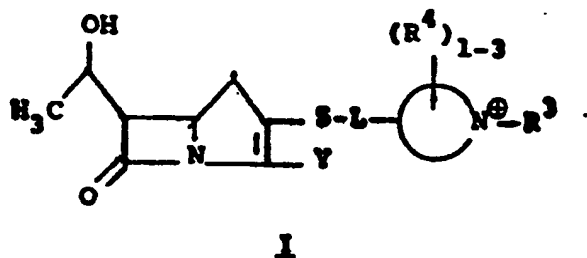
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WHAT IS CLAIMED IS:

1. A compound having the formula:



wherein:

L is a covalent bond or a bridging group selected from $-(CH_2)_{1-4}S-$; $-(CH_2)_{1-4}O-$; $-(CH_2)_{1-4}-X-(CH_2)_{1-4}$ where X is O, S, NH, or $N(C_1-C_6)alkyl$; substituted or unsubstituted C_1-C_6 straight, C_1-C_6 branched or C_3-C_7 cycloalkyl groups wherein the substituents are selected from C_1-C_6 alkyl, $O-C_1-C_6$ alkyl, $S-C_1-C_6$ alkyl, halo, OH, CF_3 , CN, NH_2 , NHC_1-C_6 alkyl, $N(C_1-C_6 alkyl)_2$, CO_2H , $CONH_2$, $CONH(C_1-C_6 alkyl)$, and $CON(C_1-C_6 alkyl)_2$;

25

$\text{---} \text{N}^+ \text{---} R^3$ is a mono- or bicyclic heteroaryl group

30 containing from 5-11 ring atoms of which up to 5 are heteroatoms wherein R^3 is:

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- 1) an unsubstituted or substituted
C₁-C₆ alkyl radical;
- 2) an unsubstituted or substituted
C₁-C₆ alkenyl radical;
- 5 3) an unsubstituted or substituted
C₁-C₆ alkynyl radical;
- 4) a C₃-C₇ cycloalkyl radical in which
the ring is substituted or
unsubstituted and one or more atoms may
10 be replaced by a heteroatom;
- 5) a C₃-C₇ cycloalkyl methyl radical
in which the ring may be substituted
and one or more atoms may be replaced
by a heteroatom;
- 15 6) an unsubstituted or substituted
C₅-C₇ cycloalkenyl radical;
- 7) an unsubstituted or substituted
bivalent C₂-C₆ alkylidene radical,
optionally interrupted by a heteroatom,
20 and joined to the heteroaryl group
to form a ring which is carbocyclic or
in which one or more atoms is replaced
by a heteroatom. The new ring may
contain one or more double bonds;
- 25 8) an unsubstituted or substituted phenyl
or heteroaryl radical;
- 9) an unsubstituted or substituted phenyl
(C₁-C₄ alkyl) or heteroaryl
(C₁-C₄ alkyl) radical;
- 30 10) a cyano (C₁-C₄ alkyl) radical;

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- 11) a carbamoyl (C_1-C_4 alkyl) radical;
- 12) a hydroxy (C_1-C_4 alkyl) radical;
- 13) an amino (C_1-C_4 alkyl) radical in which the nitrogen atom is unsubstituted or substituted with one to three C_1-C_4 alkyl groups;
- 14) an acidic side-chain of the structure $-(CH_2)_n-X-(CH_2)_m-Y-A$ where:
 - $n = 0-4$
 - $m = 0-4$
 - $X = CHR^3, CH=CH, \text{phenylene } (-C_6H_4-), NH, N(C1-C4 \text{ alkyl}), O, S, S=O, C=O, SO_2, SO_2NH, CO_2, CONH, OCO, OC=O, NHC=O;$
 - $R^3 = H, O(C1-C4 \text{ alkyl}), NH_2, NH(C1-C4 \text{ alkyl}), N(C1-C4 \text{ alkyl})_2, CN, CONH_2, CON(C1-C4 \text{ alkyl})_2, CO_2H, SO_2NH_2, SO_2NH(C1-C4 \text{ alkyl});$
 - $Y = \text{single bond}, NH, N(C1-C4 \text{ alkyl}), O, S;$
 - $A = \text{an acidic function};$

wherein the substituents in the above definitions of R^3 are independently selected from the group consisting of the definitions of R^4 set out below:

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R^4 is independently selected from:

- a) a trifluoromethyl group;
- b) a halogen atom;
- c) an unsubstituted or substituted C_1-C_4 alkoxy radical;
- d) a hydroxy group;
- e) an unsubstituted or substituted (C_1-C_6 alkyl) carbonyloxy radical;
- f) a carbamoyloxy radical which is unsubstituted or substituted on nitrogen with one or two C_1-C_4 alkyl groups;
- g) a C_1-C_6 alkylthio radical, C_1-C_6 alkylsulfinyl radical or C_1-C_6 alkylsulfonyl radical, each of which is unsubstituted or substituted on the alkyl group;
- h) a sulfamoyl group which is unsubstituted or substituted on nitrogen by one or two C_1-C_4 alkyl groups;

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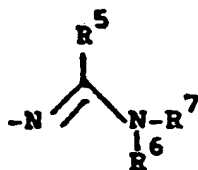
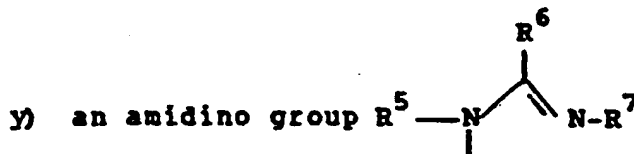
- 5
- 1) an amino group;
- j) a mono (C_1-C_4 alkyl) amino or
di(C_1-C_4 alkyl)amino group, each of
which is unsubstituted or substituted
on the alkyl group;
- k) a formylamino group;
- l) an unsubstituted or substituted
(C_1-C_6 alkyl)carbonylamino radical;
- 10 m) a (C_1-C_4 alkoxy) carbonylamino
radical;
- n) a ureido group in which the terminal
nitrogen is unsubstituted or
substituted with one or two C_1-C_4
alkyl groups;
- 15 o) a (C_1-C_6 alkyl) sulfonamido group;
- p) a cyano group;
- q) a formyl or acetalized formyl radical;
- 20 r) an unsubstituted or substituted
(C_1-C_6 alkyl)carbonyl radical
wherein the carbonyl is free or
acetalized;
- s) an unsubstituted or substituted
phenylcarbonyl or heteroarylcarbonyl
radical;
- 25 t) a hydroximinomethyl radical in which
the oxygen or carbon atom is optionally
substituted by a C_1-C_4 alkyl group;
- 30 u) a (C_1-C_6 alkoxy)carbonyl radical;
- v) a carbamoyl radical which is
unsubstituted or substituted on
nitrogen by one or two C_1-C_4 alkyl
groups;

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- w) an N-hydroxycarbamoyl or $N(C_1-C_4 \text{ alkoxy})$ carbamoyl radical in which the nitrogen atom may be additionally substituted by a C_1-C_4 alkyl group;
- x) a thiocarbamoyl group:



where R^5 , R^6 and R^7 are independently hydrogen, C_1-C_4 alkyl or wherein two of the alkyl groups together form a C_2-C_6 alkylidene radical optionally interrupted by a heteroatom and joined together to form a ring;

- z) a carboxamidino group $\begin{array}{c} NR^5 \\ || \\ C \\ \diagup \quad \diagdown \\ \quad NR^6 \quad R^7 \end{array}$. where R^5 , R^6 and R^7 are as defined above;

- aa) a guanidinyll group where R^6 in y) above is NR^8R^9 and R^8 and R^9 are as defined for R^5 through R^7 above.

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- ab) hydrogen;
- ac) an unsubstituted or substituted C_1-C_6 alkyl radical;
- ad) an unsubstituted or substituted C_1-C_6 alkenyl radical;
- ae) an unsubstituted or substituted C_1-C_6 alkynyl radical;
- af) a C_3-C_7 cycloalkyl radical in which the ring is substituted or unsubstituted and one or more atoms may be replaced by a heteroatom;
- ag) a C_3-C_7 cycloalkyl methyl radical in which the ring may be substituted and one or more atoms may be replaced by a heteroatom;
- ah) an unsubstituted or substituted C_5-C_7 cycloalkenyl radical;
- ai) an unsubstituted or substituted phenyl or heteroaryl radical;
- aj) an unsubstituted or substituted phenyl (C_1-C_4 alkyl) or heteroaryl (C_1-C_4 alkyl) radical; and

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ak) an acidic side chain of the structure

-A or $-(CH_2)_n-X-(CH_2)_m-Y-A$ where:

$n = 0-4$

$m = 0-4$

$X = CHR^2$, $CH=CH$, phenylene ($-C_6H_4-$), NH , $N(C1-C4 \text{ alkyl})$,
 O , S , $S=O$, $C=O$, SO_2 , SO_2NH , CO_2 , $CONH$, OCO_2 , $OC=O$, $NHC=O$;

$R^2 = H$, $O(C1-C4 \text{ alkyl})$, NH_2 , $NH(C1-C4 \text{ alkyl})$, $N(C1-C4 \text{ alkyl})_2$,
 CN , $CONH_2$, $CON(C1-C4 \text{ alkyl})_2$, CO_2H , SO_2NH_2 ,

$SO_2NH(C1-C4 \text{ alkyl})$;

$Y = \text{single bond}$, NH , $N(C1-C4 \text{ alkyl})$, O , S ;

$A = \text{an acidic function}$

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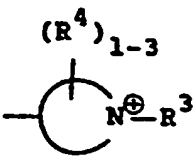
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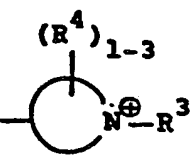
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- Y is selected from:
- i) COOH or a pharmaceutically acceptable ester or salt thereof.
 - ii) COOR¹ wherein R¹ is a removable carboxy protecting group.
 - iii) COOM wherein M is an alkali metal, or
 - iv) COO[⊖]; provided that when Y is other than iv) a counterion Z[⊖] is provided.

2. A compound of Claim 1 wherein L is substituted or unsubstituted branched or linear C₁-C₄ alkyl.

3. A compound of Claim 2 wherein  is monocyclic heteroarylium.

4. A compound of Claim 3 wherein  is a pyridinium group.

5. A compound of Claim 4 wherein R³ is an unsubstituted or substituted C₁-C₄ alkyl group.

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6. A compound of Claim 5 wherein L is

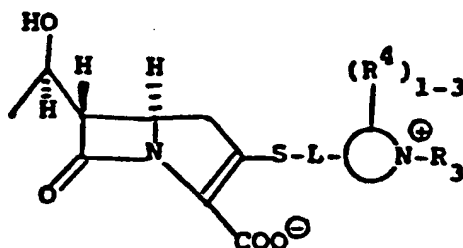
$\text{=CH}_2\text{-}$.

$\text{-CH(CH}_3\text{)-}$ or $\text{-(CH}_2\text{)}_2\text{-}$.

5

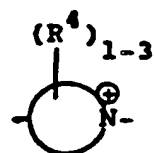
7. A compound of Claim 1 wherein the compound is a member selected from the group consisting of:

10



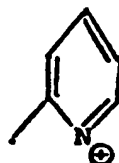
15

Com-
pound
No. L

R³

20

1 $\text{-CH}_2\text{-}$



$\text{CH}_2\text{CH}_2\text{CH}_3$

2 "

"

CH_2CH_3

25

3 "



$\text{CH}_2\text{CH}_2\text{CH}_3$

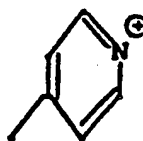
30

4 "

"

CH_2CH_3

5 "



$\text{CH}_2\text{CH}_2\text{CH}_3$

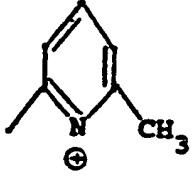
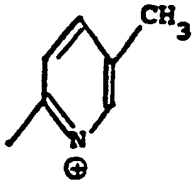
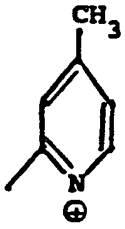
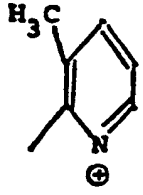
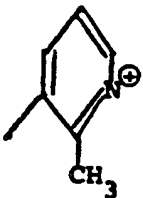
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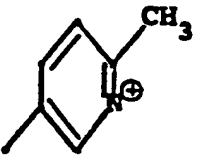
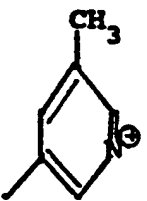
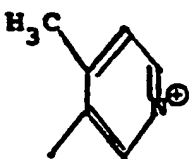

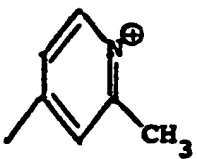

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| | | | | | |
|----|----|--------------------|---|--|---------------------------------|
| | 6 | -CH ₂ - | " | | CH ₂ CH ₃ |
| 5 | 7 | " | " | | CH ₃ |
| | | |  | | |
| 10 | 8 | " | " | | " |
| | | |  | | |
| 15 | 9 | " | " | | " |
| | | |  | | |
| 20 | | | " | | " |
| | 10 | " | " | | " |
| 25 | | |  | | |
| 30 | 11 | " | " | | " |
| | | |  | | |

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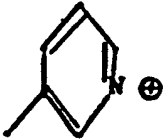


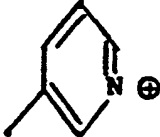

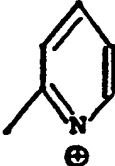
| | | | |
|----|------------------------------------|---|-----------------|
| 12 | -CH ₂ - |  | CH ₃ |
| 5 | | | |
| 13 | " |  | " |
| 10 | | | |
| 14 | " |  | " |
| 15 | | | |
| 15 | " |  | " |
| 20 | | | |
| 16 | " |  | " |
| 25 | | | |
| 17 | -CH ₂ CH ₂ - |  | " |
| 30 | | | |

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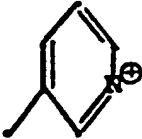
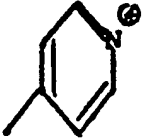
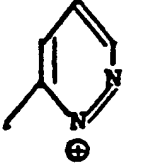
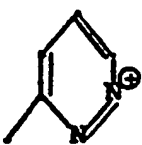
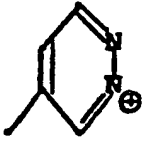
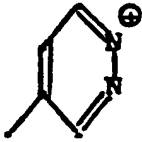
| | | | | |
|----|----|------------------------------------|---|-----------------|
| 5 | 18 | -CH ₂ CH ₂ - |  | CH ₃ |
| | 19 | " |  | " |
| 10 | 20 | -CH- CH ₃ |  | " |
| 15 | 21 | " |  | " |
| 20 | 22 | " |  | " |
| 25 | 23 | -CH ₂ - |  | CH ₂ |
| 30 | | | | |

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| | | | | |
|----|----|--------------------|---|------------------|
| 5 | 24 | -CH ₂ - |  | ØCH ₂ |
| | 25 | " |  | " |
| 10 | 26 | " |  | CH ₃ |
| 15 | 27 | " |  | " |
| 20 | 28 | " |  | " |
| 25 | 29 | " |  | " |
| 30 | | | | |

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| | | | |
|----|-----------------------|--|-------------------|
| 5 | 30 -CH ₂ - | | CH ₃ . |
| 10 | 31 " | | " |
| 15 | 32 " | | " |
| 20 | 33 " | | " |
| 25 | 34 " | | " |
| 30 | 35 " | | " |

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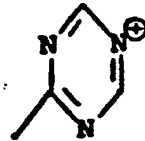
36 -CH₂-



CH₃

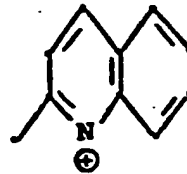
5

37 "



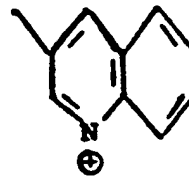
10

38 "



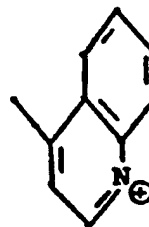
15

39 "



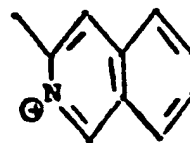
20

25 40 "



30

41 "



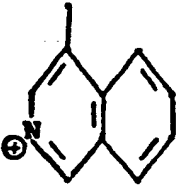

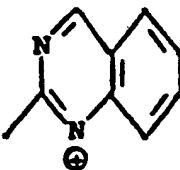
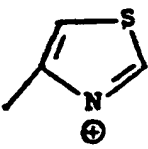
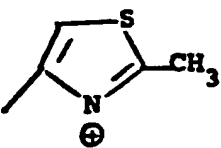
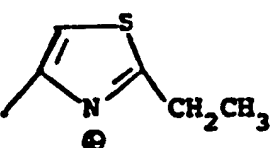
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| | | | | |
|----|----|--------------------|---|---|
| 5 | 42 | -CH ₂ - |  | CH ₃ |
| 10 | 43 | " |  | " |
| 15 | 44 | " |  | " |
| 20 | 45 | " |  | CH ₂ CH ₂ CH ₃ |
| 25 | 46 | " | " | CH ₂ CH ₃ |
| 30 | 47 | " |  | CH ₃ |
| | 48 | " |  | " |

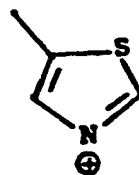
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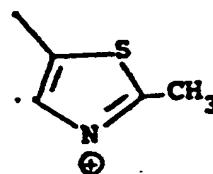
49 -CH₂-

5

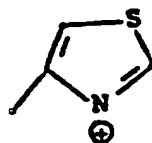
CH₃

50 "

10

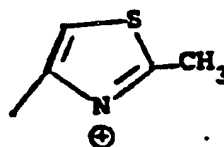
51 -CH-
CH₃

15

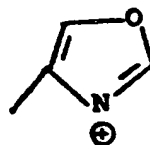


52 "

20

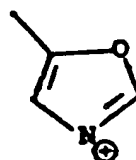
53 -CH₂-

25



54 "

30

CH₂CH₃

55 "

CH₃

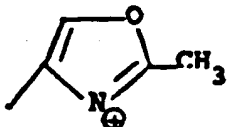
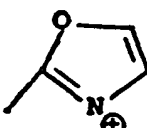

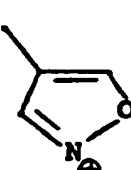

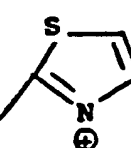
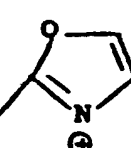
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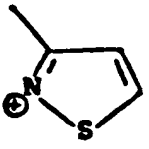
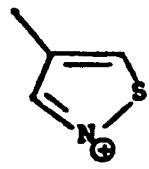
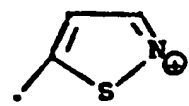
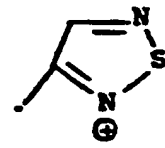
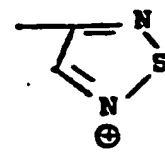
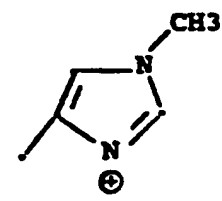
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| | | | | |
|----|----|------------------------------------|---|-----------------|
| | 56 | -CH ₂ - |  | CH ₃ |
| 5 | 57 | " |  | " |
| 10 | 58 | " |  | " |
| 15 | 59 | " |  | " |
| 20 | 60 | " |  | " |
| 25 | 61 | " |  | " |
| 30 | 62 | -CH ₂ CH ₂ - |  | " |

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| | | | | |
|----|----|--------------------|--|--|
| 5 | 63 | -CH ₂ - |  | CH ₃ |
| | 64 | " |  | " |
| 10 | 65 | " |  | " |
| 15 | 66 | " |  | " |
| 20 | 67 | " |  | " |
| 25 | 68 | " |  | -CH ₂ CH ₂ CH ₃ |
| 30 | 69 | " | " | -CH ₂ CH ₃ |

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| | | | |
|----|-----------------------|---|---|
| 5 | 70 -CH ₂ - | | -CH ₃ . |
| 10 | 71 " | | " |
| 15 | 72 " | | " |
| 20 | 73 " | | " |
| 25 | 74 " | | CH ₂ OCH ₃ |
| | 75 " | " | CH ₂ CN |
| 30 | 76 " | " | CH ₂ CO ₂ H |
| | 77 " | " | CH ₂ SO ₂ CH ₃ |

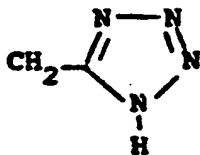

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| | | | | |
|----|----|--------------------|---|---|
| | 78 | -CH ₂ - | " | $\text{CH}_2\overset{\text{O}}{\underset{\text{O}}{\text{P}}}(\text{OH})\text{OCH}_3$ |
| 5 | 79 | " | " | $\text{CH}_2\text{SO}_3\text{H}$ |
| | 80 | " | " | $\text{CH}_2\text{CONMe}_2$ |
| | 81 | " | " | CH_2SOCH_3 |
| 10 | 82 | " | " | CH_2NMe_2 |
| 15 | 83 | " | " |  |
| 20 | 84 | " |  | CH_2OCH_3 |
| | 85 | " | " | CH_2SCH_3 |
| 25 | 86 | " | " | CH_2SOCH_3 |
| | 87 | " | " | $\text{CH}_2\text{SO}_2\text{CH}_3$ |
| 30 | 88 | " | " | $\text{CH}_2\text{CO}_2\text{H}$ |
| | 89 | " | " | $\text{CH}_2\text{CONMe}_2$ |

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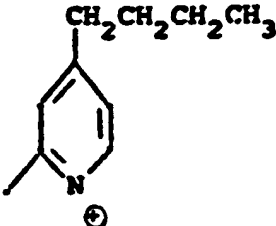


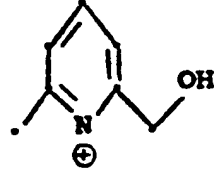
| | | | | |
|----|-----|--------------------|---|---|
| | 90 | -CH ₂ - | " | $\text{CH}_2\overset{\text{O}}{\underset{\uparrow}{\text{P}}}(\text{OH})\text{OCH}_3$ |
| 5 | 91 | " | " | $\text{CH}_2\text{SO}_3\text{H}$ |
| | 92 | " | " | CH_2CN |
| | 93 | " | " | CH_2NMe_2 |
| 10 | 94 | " | " | $\text{CH}_2\text{CH}_2\text{NMe}_2$ |
| 15 | 95 | " |  | CH_2OCH_3 |
| | 96 | " | " | CH_2NMe_2 |
| 20 | 97 | " | " | $\text{CH}_2\text{CH}_2\text{NMe}_2$ |
| | 98 | " | " | CH_2CN |
| | 99 | " | " | CH_2SCH_3 |
| 25 | 100 | " | " | CH_2SOCH_3 |
| | 101 | " | " | $\text{CH}_2\text{SO}_2\text{CH}_3$ |
| 30 | 102 | " | " | $\text{CH}_2\text{CO}_2\text{H}$ |
| | 103 | " | " | $\text{CH}_2\text{CONMe}_2$ |

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| | | | | |
|----|-----|--|--|---|
| | 104 | -CH ₂ - | " | $\text{CH}_2\overset{\text{O}}{\underset{\text{O}}{\text{P}}}(\text{OH})\text{OCH}_3$ |
| 5 | 105 | " | " | $\text{CH}_2\text{SO}_3\text{H}$ |
| | 106 | " |  | CH_3 |
| 10 | | | | |
| 15 | 107 | -CH ₂ CH ₂ CH ₂ - |  | " |
| 20 | 108 | -CH ₂ CH- CH ₂ OH |  | " |
| 25 | 109 | -CH ₂ - |  | " |
| 30 | | | | |

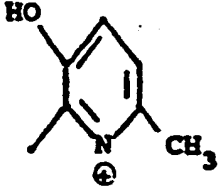
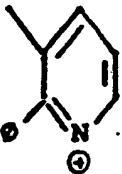

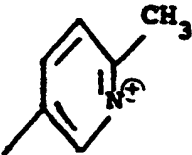
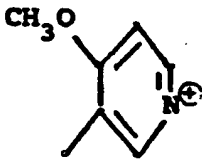
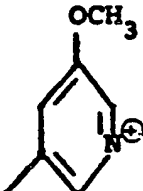
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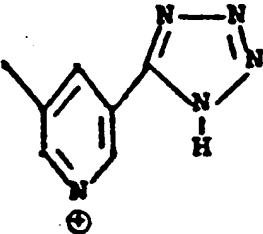

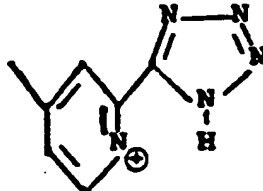



| | | | |
|----|--|---|-----------------|
| 5 | 110 -CH ₂ - |  | CH ₃ |
| 10 | 111 " |  | " |
| 15 | 112 -CH ₂ CH ₂ CH ₂ - |  | " |
| 20 | 113 -CH ₂ CH ₂ - |  | " |
| 25 | 114 -CH ₂ - |  | " |
| 30 | 115 " |  | " |

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| | | | |
|----|--|---|---------------------------------|
| 5 | 116 -CH ₂ - |  | CH ₃ |
| 10 | 117 -CH ₂ CH ₂ CH ₂ - |  | " |
| 15 | 118 CH ₂ |  | " |
| 20 | 119 bond |  | " |
| 25 | 120 " |  | " |
| 30 | 121 " |  | CH ₂ CH ₃ |

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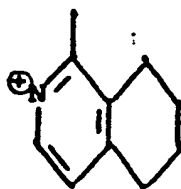
122 bond



CH₃

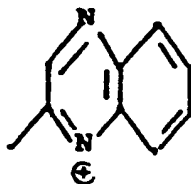
5

123 -CH₂-



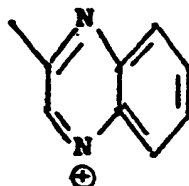
10

124 "



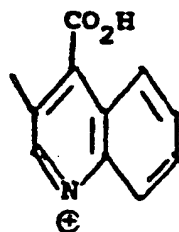
15

125 "



20

25 126 "



30

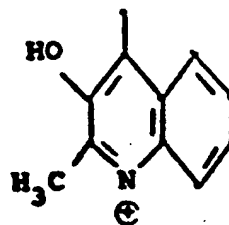
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127 -CH₂-

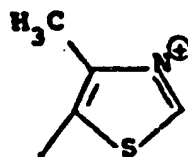
5



CH₃

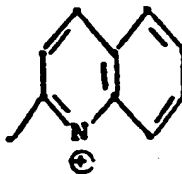
128 -CH₂CH₂-

10

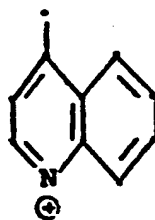


129 bond

15

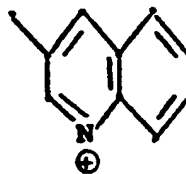


20 130



25

131



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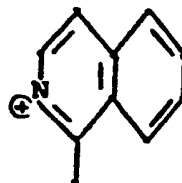
132 bond



CH₃

5

133 "



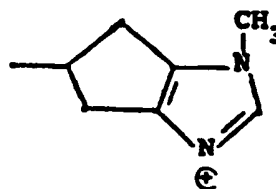
10

134 "



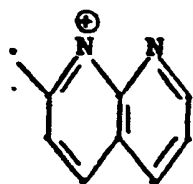
15

135 "



20

136 -CH-
CH₃



25

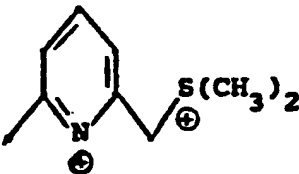
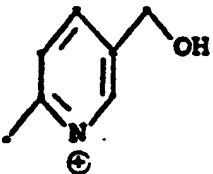
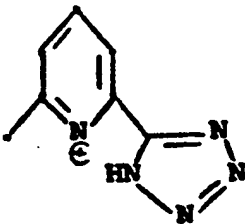
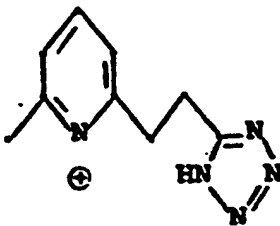
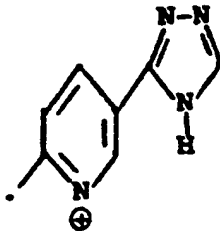
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| | | | | |
|----|-----|--------------------|--|-----------------|
| 5 | 137 | -CH ₂ - |  | CH ₃ |
| 10 | 138 | " |  | " |
| 15 | 139 | " |  | " |
| 20 | 140 | " |  | " |
| 25 | | | | |
| 30 | 141 | " |  | " |

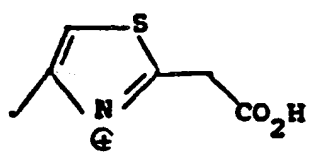
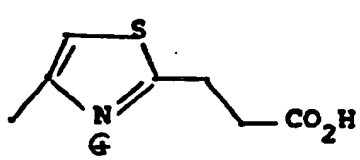
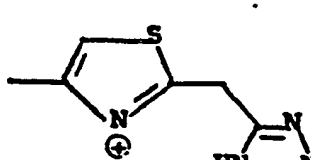
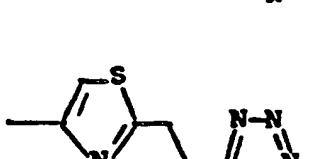

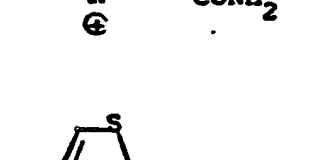
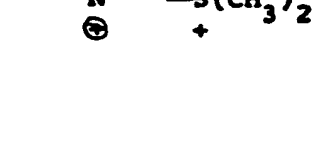
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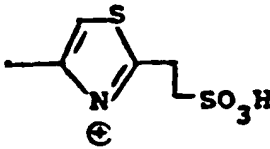
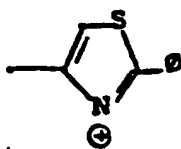
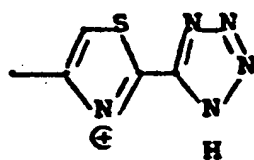
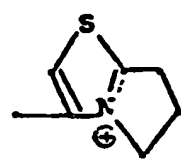
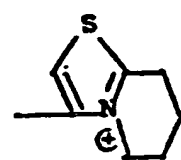

| | | | | |
|----|-----|-----------------|--|-----------------|
| 5 | 142 | CH ₂ |  | CH ₃ |
| | 143 | " |  | " |
| 10 | 144 | " |  | " |
| 15 | 145 | " |  | " |
| 20 | 146 | " |  | " |
| 25 | 147 | " |  | " |
| 30 | 147 | " |  | " |

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| | | | |
|-----|--------------------|---|-----------------|
| 148 | -CH ₂ - |  | CH ₃ |
| 149 | " |  | " |
| 150 | " |  | " |
| 151 | " |  | -- |
| 152 | " |  | -- |
| 153 | " |  | -- |

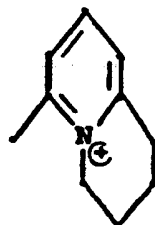
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5 154 -CH₂-



10 155 "



15 156 "



20 157 "

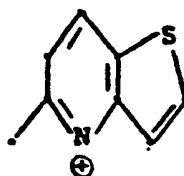


25 158 $\begin{matrix} \text{CH}_3 \\ | \\ -\text{CHCH}_2- \end{matrix}$



CH₃

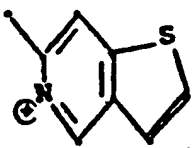
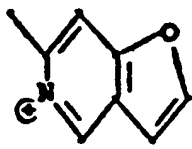
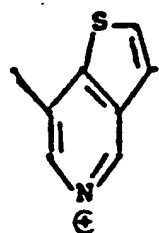
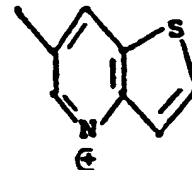
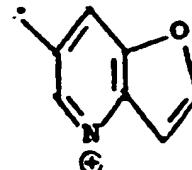
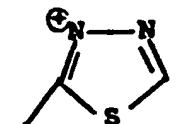
30 159 -CH₂-



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| | | | |
|-----|--------------------|---|-----------------|
| 160 | -CH ₂ - |  | CH ₃ |
| 5 | | | |
| 161 | " |  | " |
| 10 | | | |
| 162 | " |  | " |
| 15 | | | |
| 163 | " |  | " |
| 20 | | | |
| 164 | " |  | " |
| 25 | | | |
| 165 | " |  | " |
| 30 | | | |

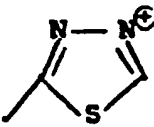
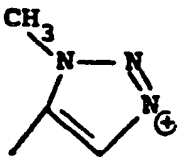

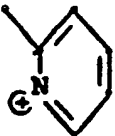

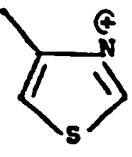
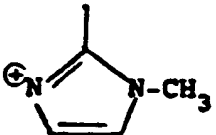
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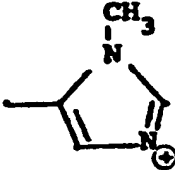
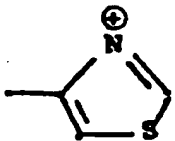

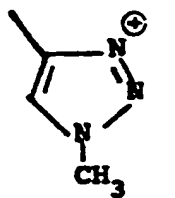
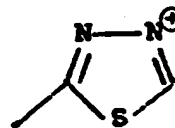
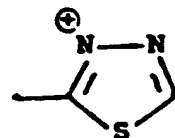
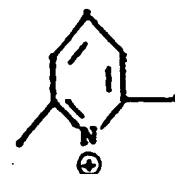
| | | | | |
|----|-----|--------------------|---|-----------------------------------|
| | 166 | -CH ₂ - |  | CH ₃ |
| 5 | 167 | " |  | " |
| 10 | 168 | " |  | CH ₂ CONH ₂ |
| 15 | 169 | " |  | " |
| 20 | 170 | " |  | " |
| 25 | 171 | " |  | " |
| 30 | 172 | bond |  | CH ₃ |

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| | | | | |
|----|-----|------|--|-----------------|
| | 173 | bond |  | CH ₃ |
| 5 | | | | |
| | 174 | " |  | " |
| 10 | | | | |
| | 175 | " |  | " |
| 15 | | | | |
| | 176 | " |  | " |
| 20 | | | | |
| | 177 | " |  | " |
| 25 | | | | |
| | 178 | " |  | " |
| 30 | | | | |
| | 179 | " |  | " |

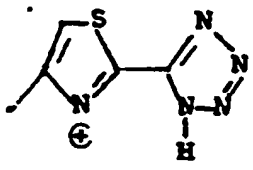
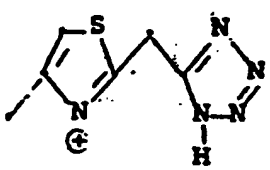
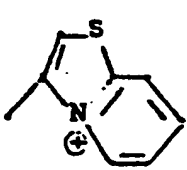
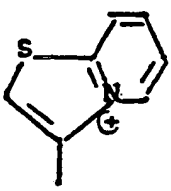
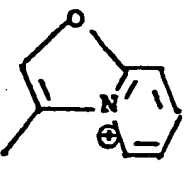
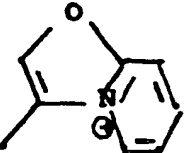
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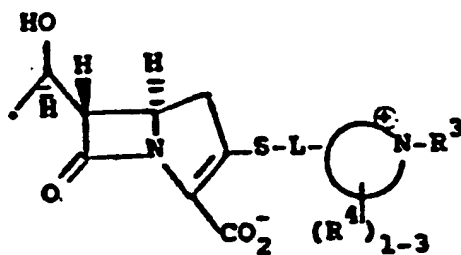
| | | | |
|----|------------------------|---|-----------------|
| 5 | 180 -CH ₂ - |  | CH ₃ |
| 10 | 181 " |  | " |
| 15 | 182 " |  | -- |
| 20 | 183 bond |  | -- |
| 25 | 184 CH ₂ |  | -- |
| 30 | 185 bond |  | -- |

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10

| Compound No. | L | $(R^4)_{1-3}$  | R_3 | R_4 |
|-----------------|-------------------|--|-----------------|---------------------------------|
| 15 | 1 CH ₂ |  | CH ₃ | CO ₂ H |
| 20 | 2 | " | " | CONH ₂ |
| 3 | " | " | " | CN |
| 25 | 4 | " | " | OH |
| 5 | " | " | " | SO ₂ NH ₂ |
| 30 | 6 | " | " | SO ₃ H |
| 7 | " | " | " | NMe ₂ |
| 8 | " | " | " | CONMe ₂ |

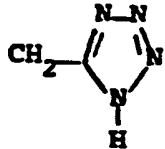
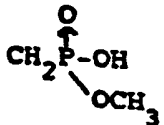
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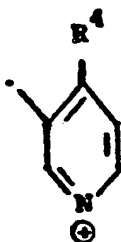
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| | 9 | " | " | " | CH_2NMe_2 |
| | 10 | " | " | " | CH_2CN |
| 5 | 11 | " | " | " | CH_2CONH_2 |
| | 12 | " | " | " | $\text{CH}_2\text{CO}_2\text{H}$ |
| 10 | 13 | " | " | " | CH_2SCH_3 |
| | 14 | " | " | " | CH_2SOCH_3 |
| | 15 | " | " | " | $\text{CH}_2\text{SO}_2\text{CH}_3$ |
| 15 | 16 | " | " | " | SO_2CH_3 |
| | 17 | " | " | " | SOCH_3 |
| 20 | 18 | " | " | " |  |
| 25 | 19 | " | " | " | $\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$ |
| | 20 | " | " | " | $\text{CH}_2\text{SO}_3\text{H}$ |
| | 21 | " | " | " | CH_2OCH_3 |
| 30 | 22 | " | " | " |  |

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| | | | | | |
|----|----|---|---|---|---|
| | 23 | " | " | " | CH ₂ CH ₂ SO ₃ H |
| | 24 | " | " | " | CF ₃ |
| 5 | 25 | " | " | " | CH ₂ OC(=O)NH ₂ |
| | 26 | " | " | " | CH ₂ SO ₂ NH ₂ |
| 10 | 27 | " | " | " | Br |
| | 28 | " | " | " | Cl |
| | 29 | " | " | " | F |
| 15 | 30 | " | " | " | CO ₂ H |
| 20 | | | | | |
| | 31 | " | " | " | CONH ₂ |
| 25 | 32 | " | " | " | CN |
| | 33 | " | " | " | OH |
| | 34 | " | " | " | SONH ₂ |
| 30 | | | | | |



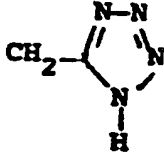
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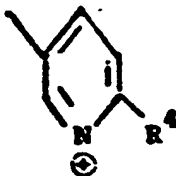
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| | | | | | |
|----|----|---|---|---|---|
| | 35 | " | " | " | SO ₃ H |
| | 36 | " | " | " | NMe ₂ |
| 5 | 37 | " | " | " | CONMe ₂ |
| | 38 | " | " | " | CH ₂ NMe ₂ |
| | 39 | " | " | " | CH ₂ CN |
| 10 | 40 | " | " | " | CH ₂ CONH ₂ |
| | 41 | " | " | " | CH ₂ CO ₂ H |
| 15 | 41 | " | " | " | CH ₂ SCH ₃ |
| | 43 | " | " | " | CH ₂ SOCH ₃ |
| | 44 | " | " | " | CH ₂ SO ₂ CH ₃ |
| 20 | 45 | " | " | " | SO ₂ CH ₃ |
| | 46 | " | " | " | SOCH ₃ |
| 25 | 47 | " | " | " |  |
| 30 | 48 | " | " | " | CH ₂ CH ₂ CO ₂ H |
| | 49 | " | " | " | CH ₂ SO ₃ H |
| | 50 | " | " | " | CH ₂ OCH ₃ |

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| | | | | | |
|----|----|---|--|---|--|
| | 51 | " | " | " | $\text{CH}_2\overset{\text{O}}{\underset{\text{OCH}_3}{\text{P}}}\text{-OH}$ |
| 5 | 52 | " | " | " | $\text{CH}_2\text{CH}_2\text{SO}_3\text{H}$ |
| | 53 | " | " | " | CF_3 |
| 10 | 54 | " | " | " | $\text{CH}_2\overset{\text{O}}{\parallel}\text{OCNH}_2$ |
| | 55 | " | " | " | $\text{CH}_2\text{SO}_2\text{NH}_2$ |
| | 56 | " | " | " | $\text{CH}_2\text{SO}_2\text{NMe}_2$ |
| 15 | 57 | " |  | " | CO_2H |
| 20 | 58 | " | " | " | CONH_2 |
| | 59 | " | " | " | CN |
| 25 | 60 | " | " | " | OCH_3 |
| | 61 | " | " | " | SO_2NH_2 |
| 30 | 62 | " | " | " | SO_3H |
| | 63 | " | " | " | NMe_2 |

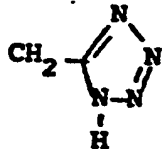
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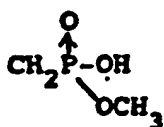
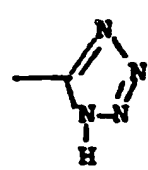
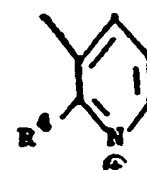
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| | | | | | |
|----|----|---|---|---|---|
| | 64 | " | " | " | CONMe ₂ |
| | 65 | " | " | " | CH ₂ NMe ₂ |
| 5 | 66 | " | " | " | CH ₂ CN |
| | 67 | " | " | " | CH ₂ CONH ₂ |
| 10 | 68 | " | " | " | CH ₂ CO ₂ H |
| | 69 | " | " | " | CH ₂ SCH ₃ |
| | 70 | " | " | " | CH ₂ SOCH ₃ |
| 15 | 71 | " | " | " | CH ₂ SO ₂ CH ₃ |
| | 72 | " | " | " | SO ₂ CH ₃ |
| 20 | 73 | " | " | " | SOCH ₃ |
| | 74 | " | " | " | CH ₂ -  |
| 25 | 75 | " | " | " | CH ₂ CH ₂ CO ₂ H |
| | 76 | " | " | " | CH ₂ SO ₃ H |
| 30 | 77 | " | " | " | CH ₂ OCH ₃ |

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| | | | | | |
|----|----|---|---|---|--|
| | 78 | " | " | " |  |
| 5 | 79 | " | " | " | $\text{CH}_2\text{CH}_2\text{SO}_3\text{H}$ |
| | 80 | " | " | " | CF_3 |
| 10 | 81 | " | " | " | CH_2OCNH_2 |
| | 82 | " | " | " | $\text{CH}_2\text{SO}_2\text{NH}_2$ |
| 15 | 83 | " | " | " | $\text{CH}_2\text{SO}_2\text{NMe}_2$ |
| | 84 | " | " | " |  |
| 20 | | | | | |
| | 85 | " |  | " | CO_2H |
| 25 | | | | | |
| | 86 | " | " | " | CONH_2 |
| | 87 | " | " | " | CN |
| 30 | | | | | |
| | 88 | " | " | " | OCH_3 |

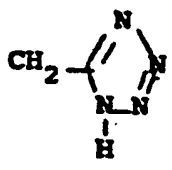
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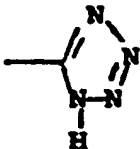

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|----|-----|-----------------|---|---|---|
| | 89 | " | " | " | SO ₂ NH ₂ |
| | 90 | " | " | " | SO ₃ H |
| 5 | 91 | " | " | " | NMe ₂ |
| | 92 | " | " | " | CONMe ₂ |
| 10 | 93 | " | " | " | CH ₂ NMe ₂ |
| | 94 | " | " | " | CH ₂ CN |
| | 95 | " | " | " | CH ₂ CONH ₂ |
| 15 | 96 | " | " | " | CH ₂ CO ₂ H |
| | 97 | " | " | " | CH ₂ SCH ₃ |
| 20 | 98 | " | " | " | CH ₂ SOCH ₃ |
| | 99 | CH ₃ | " | " | CH ₂ SO ₂ CH ₃ |
| | 100 | " | " | " | SO ₂ CH ₃ |
| 25 | 101 | " | " | " | SOCH ₃ |
| 30 | 102 | " | " | " |  |
| | 103 | " | " | " | CH ₂ CH ₂ CO ₂ H |

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| | | | | | |
|----|-----|-----------------|---|---|---|
| | 104 | " | " | " | $\text{CH}_2\text{SO}_3\text{H}$ |
| | 105 | " | " | " | CH_2OCH_3 |
| 5 | 106 | " | " | " | $\text{CH}_2\overset{\text{O}}{\underset{\text{OCH}_3}{\text{P}}}-\text{OH}$ |
| | 107 | " | " | " | $\text{CH}_2\text{CH}_2\text{SO}_3\text{H}$ |
| 10 | 108 | " | " | " | CF_3 |
| | 109 | " | " | " | $\text{CH}_2\overset{\text{O}}{\parallel}\text{CONH}_2$ |
| 15 | 110 | " | " | " | $\text{CH}_2\text{SO}_2\text{NH}_2$ |
| | 111 | " | " | " | $\text{CH}_2\text{SO}_2\text{NMe}_2$ |
| 20 | 112 | " | " | " |  |
| 25 | 113 | $-\text{CH}_2-$ |  | " | CO_2H |
| 30 | 114 | " | " | " | CONH_2 |
| | 115 | " | " | " | CN |

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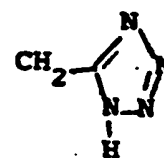
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| | | | | | |
|----|-----|---|---|---|---|
| | 116 | " | " | " | OCH ₃ |
| | 117 | " | " | " | SO ₂ NH ₂ |
| 5 | 118 | " | " | " | SO ₃ H |
| | 119 | " | " | " | NMe ₂ |
| | 120 | " | " | " | CONMe ₂ |
| 10 | 121 | " | " | " | CH ₂ NMe ₂ |
| | 122 | " | " | " | CH ₂ CN |
| 15 | 123 | " | " | " | CH ₂ CONH ₂ |
| | 124 | " | " | " | CH ₂ CO ₂ H |
| | 125 | " | " | " | CH ₂ SCH ₃ |
| 20 | 126 | " | " | " | CH ₂ SOCH ₃ |
| | 127 | " | " | " | CH ₂ SO ₂ CH ₃ |
| 25 | 128 | " | " | " | SO ₂ CH ₃ |
| | 129 | " | " | " | SOCH ₃ |


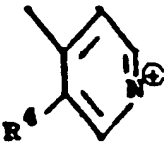
30 130 "



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| | | | | | |
|----|-----|---|---|---|--|
| | 131 | " | " | " | $\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$ |
| | 132 | " | " | " | $\text{CH}_2\text{SO}_3\text{H}$ |
| 5 | 133 | " | " | " | CH_2OCH_3 |
| | 134 | " | " | " | $\begin{array}{c} \text{O} \\ \uparrow \\ \text{CH}_2\text{P}-\text{OH} \\ \quad \quad \quad \backslash \\ \quad \quad \quad \text{OCH}_3 \end{array}$ |
| 10 | 135 | " | " | " | $\text{CH}_2\text{CH}_2\text{SO}_3\text{H}$ |
| | 136 | " | " | " | CF_3 |
| 15 | 137 | " | " | " | $\text{CH}_2\text{OC(=O)NH}_2$ |
| | 138 | " | " | " | $\text{CH}_2\text{SO}_2\text{NH}_2$ |
| 20 | 139 | " | " | " | $\text{CH}_2\text{SO}_2\text{NMe}_2$ |
| | 140 | " | " | " |  |
| 25 | | | | | |
| | 141 | " |  | " | CO_2H |
| 30 | | | | | |
| | 142 | " | " | " | CONH_2 |

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| | | | | | |
|----|-----|---|---|---|---|
| | 143 | " | " | " | CN |
| | 144 | " | " | " | OH |
| 5 | 145 | " | " | " | OCH ₃ |
| | 146 | " | " | " | SO ₂ NH ₂ |
| 10 | 147 | " | " | " | SO ₃ H |
| | 148 | " | " | " | NMe ₂ |
| | 149 | " | " | " | CONMe ₂ |
| 15 | 150 | " | " | " | CH ₂ NMe ₂ |
| | 151 | " | " | " | CH ₂ CN |
| 20 | 152 | " | " | " | CH ₂ CONH ₂ |
| | 153 | " | " | " | CH ₂ CO ₂ H |
| | 154 | " | " | " | CH ₂ SCH ₃ |
| 25 | 155 | " | " | " | CH ₂ SOCH ₃ |
| | 156 | " | " | " | CH ₂ SO ₂ CH ₃ |
| 30 | 157 | " | " | " | SO ₂ CH ₃ |
| | 158 | " | " | " | SOCH ₃ |

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159 "

5 160 "

161 "

10 162 "

163 "

15 164 "

165 "

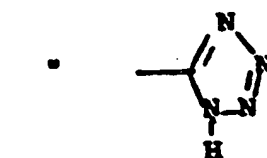
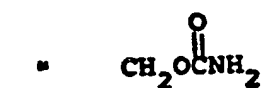
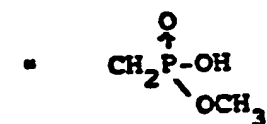
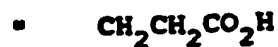
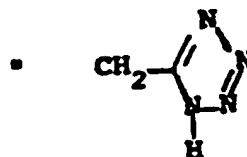
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167 "

25 168 "

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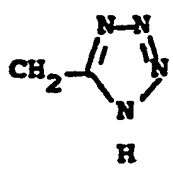
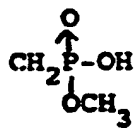

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| | | | | | |
|----|-----|---|---|---|-----------------------------------|
| | 170 | " | " | " | F |
| | 171 | " | " | " | Cl |
| 5 | 172 | " | " | " | Br |
| 10 | 173 | " |  | " | CO ₂ H |
| | 174 | " | " | " | CONH ₂ |
| 15 | 175 | " | " | " | CN |
| | 176 | " | " | " | SO ₂ NH ₂ |
| 20 | 177 | " | " | " | SO ₃ H |
| | 178 | " | " | " | NMe ₂ |
| | 179 | " | " | " | CONMe ₂ |
| 25 | 180 | " | " | " | CH ₂ NMe ₂ |
| | 181 | " | " | " | CH ₂ CN |
| 30 | 182 | " | " | " | CH ₂ CONH ₂ |
| | 183 | " | " | " | CH ₂ CO ₂ H |

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| | | | | | |
|----|-----|---|---|---|---|
| | 184 | " | " | " | CH_2SCH_3 |
| | 185 | " | " | " | CH_2SOCH_3 |
| 5 | 186 | " | " | " | $\text{CH}_2\text{SO}_2\text{CH}_3$ |
| | 187 | " | " | " | SO_2CH_3 |
| 10 | 188 | " | " | " |  |
| | 189 | " | " | " | $\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$ |
| 15 | 190 | " | " | " | $\text{CH}_2\text{SO}_3\text{H}$ |
| | 191 | " | " | " | CH_2OCH_3 |
| 20 | 192 | " | " | " |  |
| | 193 | " | " | " | $\text{CH}_2\text{CH}_2\text{SO}_3\text{H}$ |
| 25 | 194 | " | " | " | CF_3 |
| | 195 | " | " | " |  |
| 30 | 196 | " | " | " | $\text{CH}_2\text{SO}_2\text{NH}_2$ |


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| | | | | | |
|----|--------|---|---|---|-----------------------------------|
| 5 | 197 | " |  | " | CO ₂ H |
| | 198 | " | | " | CONH ₂ |
| | 10 199 | " | | " | CN |
| | 200 | " | | " | OH |
| | 201 | " | | " | SO ₂ NH ₂ |
| 15 | 202 | " | " | " | SO ₃ H |
| | 203 | " | " | " | NMe ₂ |
| | 20 204 | " | " | " | CONMe ₂ |
| 25 | 205 | " | " | " | CH ₂ NMe ₂ |
| | 206 | " | " | " | CH ₂ CN |
| | 207 | " | " | " | CH ₂ CONH ₂ |
| | 208 | " | " | " | CH ₂ CO ₂ H |
| 30 | 209 | " | " | " | CH ₂ SCH ₃ |
| | 210 | " | " | " | CH ₂ SOCH ₃ |

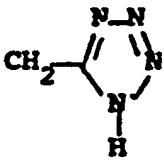
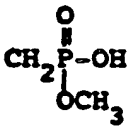
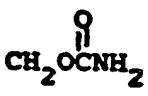
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| | | | | | |
|----|-----|---|---|---|---|
| | 211 | " | " | " | $\text{CH}_2\text{SO}_2\text{CH}_3$ |
| | 212 | " | " | " | SO_2CH_3 |
| 5 | 213 | " | " | " | SOCH_3 |
| | 214 | " | " | " |  |
| 10 | 215 | " | " | " | $\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$ |
| | 216 | " | " | " | $\text{CH}_2\text{SO}_3\text{H}$ |
| 15 | 217 | " | " | " | CH_2OCH_3 |
| | 218 | " | " | " |  |
| 20 | 219 | " | " | " | $\text{CH}_2\text{CH}_2\text{SO}_3\text{H}$ |
| | 220 | " | " | " | CF_3 |
| 25 | 221 | " | " | " |  |
| | 222 | " | " | " | $\text{CH}_2\text{SO}_2\text{NH}_2$ |
| 30 | 223 | " | " | " | Br |

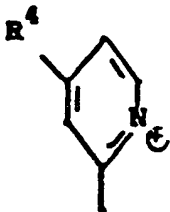
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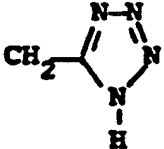
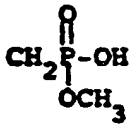
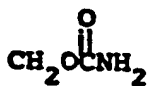
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|----|-----|---|---|---|-----------------------------------|
| | 224 | " | " | " | Cl |
| | 225 | " | " | " | F |
| 5 | 226 | " |  | " | CO ₂ H |
| 10 | 227 | " | " | " | CONH ₂ |
| | 228 | " | " | " | CN |
| 15 | 229 | " | " | " | SO ₂ NH ₂ |
| | 230 | " | " | " | SO ₃ H |
| | 231 | " | " | " | NMe ₂ |
| 20 | 232 | " | " | " | CONMe ₂ |
| | 233 | " | " | " | CH ₂ NMe ₂ |
| 25 | 234 | " | " | " | CH ₂ CN |
| | 235 | " | " | " | CH ₂ CONH ₂ |
| | 236 | " | " | " | CH ₂ CO ₂ H |
| 30 | 237 | " | " | " | CH ₂ SCH ₃ |

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| | | | | | |
|----|-----|---|---|---|---|
| | 238 | " | " | " | CH_2SOCH_3 |
| | 239 | " | " | " | $\text{CH}_2\text{SO}_2\text{CH}_3$ |
| 5 | 240 | " | " | " | SO_2CH_3 |
| | 241 | " | " | " | SOCH_3 |
| 10 | 242 | " | " | " |  |
| | 243 | " | " | " | $\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$ |
| 15 | 244 | " | " | " | $\text{CH}_2\text{SO}_3\text{H}$ |
| | 245 | " | " | " | CH_2OCH_3 |
| 20 | 246 | " | " | " |  |
| | 247 | " | " | " | $\text{CH}_2\text{CH}_2\text{SO}_3\text{H}$ |
| 25 | 248 | " | " | " | CF_3 |
| | 249 | " | " | " |  |
| 30 | 250 | " | " | " | $\text{CH}_2\text{SO}_2\text{NH}_2$ |

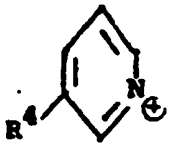
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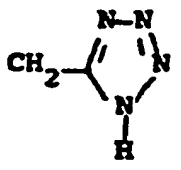
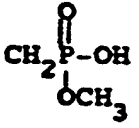
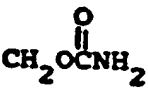
| | | | | | |
|----|-----|---|---|---|-----------------------------------|
| | 251 | " |  | " | CO ₂ H |
| 5 | | | . | | |
| | 252 | " | " | " | CONH ₂ |
| | 253 | " | " | " | CN |
| 10 | | | | | |
| | 254 | " | " | " | OH |
| | 255 | " | " | " | SO ₂ NH ₂ |
| 15 | 256 | " | " | " | SO ₃ H |
| | 257 | " | " | " | NMe ₂ |
| | 258 | " | " | " | CONMe ₂ |
| 20 | | | | | |
| | 259 | " | " | " | CH ₂ NMe ₂ |
| | 260 | " | " | " | CH ₂ CN |
| 25 | 261 | " | " | " | CH ₂ CONH ₂ |
| | 262 | " | " | " | CH ₂ CO ₂ H |
| | 263 | " | " | " | CH ₂ SCH ₃ |
| 30 | | | | | |
| | 264 | " | " | " | CH ₂ SOCH ₃ |

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| | | | | | |
|----|-----|---|---|---|--|
| | 265 | " | " | " | $\text{CH}_2\text{SO}_2\text{CH}_3$ |
| | 266 | " | " | " | SO_2CH_3 |
| 5 | 267 | " | " | " | SOCH_3 |
| 10 | 268 | " | " | " |  <chem>CN1C=NC=N1</chem> |
| | 269 | " | " | " | $\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$ |
| | 270 | " | " | " | $\text{CH}_2\text{SO}_3\text{H}$ |
| 15 | 271 | " | " | " | CH_2OCH_3 |
| 20 | 272 | " | " | " |  <chem>COP(=O)(O)C</chem> |
| | 273 | " | " | " | $\text{CH}_2\text{CH}_2\text{SO}_3\text{H}$ |
| 25 | 274 | " | " | " | CF_3 |
| | 275 | " | " | " |  <chem>NC(=O)C</chem> |
| 30 | 276 | " | " | " | $\text{CH}_2\text{SO}_2\text{NH}_2$ |

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| | | | | | |
|---|-----|---|---|---|----|
| | 277 | " | " | " | Br |
| | 278 | " | " | " | Cl |
| 5 | 279 | " | " | " | F |

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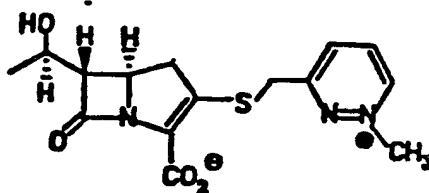
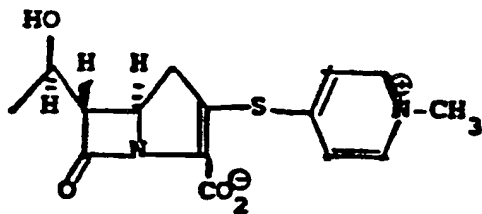
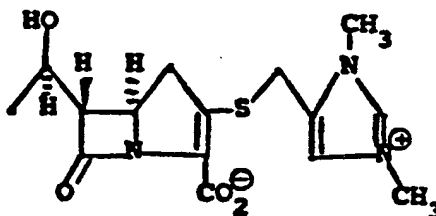
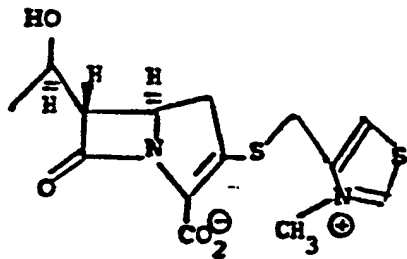
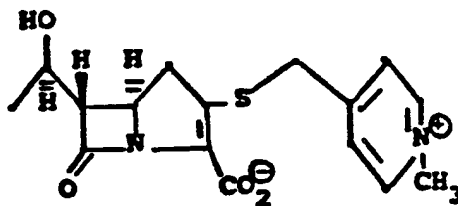
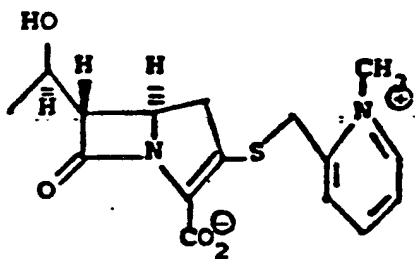
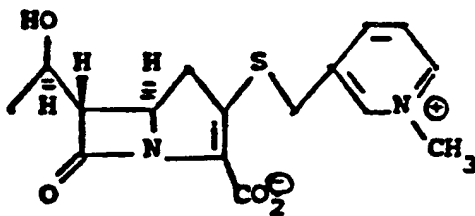
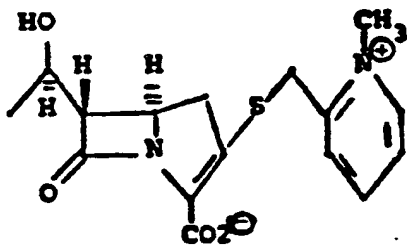
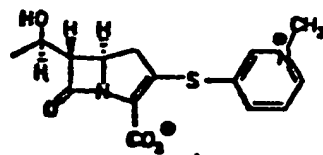
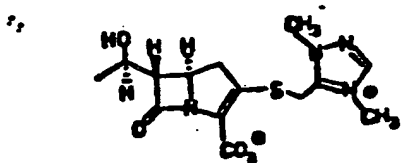
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8. A compound of Claim 1 wherein the compound is a member selected from the group consisting of:



9. The combination of a compound of Claim 1 and a DHP inhibitor.

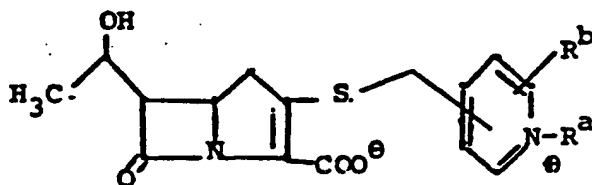
10. A combination of Claim 9 wherein the DHP inhibitor is 7-(1-2-amino-2-carboxyethylthio)-2-(2,2-dimethylcyclopropanecarboxamide)-2-heptenoic acid.

11. A pharmaceutical composition for antibiotic use comprising an antibacterially effective amount of a compound of Claim 1, an inhibitorily effective amount of a DHP inhibitor, and, optionally, a pharmaceutically acceptable carrier.

12. A pharmaceutical composition according to Claim 11 wherein the DHP inhibitor is 7-(1-2-amino-2-carboxyethylthio)-2-(2,2-dimethylcyclopropanecarboxamide)-2-heptenoic acid.

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13. A compound of Claim 1 of the structure:



wherein

R^a is C_{1-4} alkyl; or an acidic sidechain of the structure $-(CH_2)_n-X-(CH_2)_m-Y-A$ where:

$n = 0-4$

$m = 0-4$

$X = CHR^3, CH=CH, \text{phenylene } (-C_6H_4-), NH, N(C1-C4 \text{ alkyl}), O, S, S=O, C=O, SO_2, SO_2NH, CO_2, CONH, OCO_2, OC=O, NHC=O;$

$R^3 = H, O(C1-C4 \text{ alkyl}), NH_2, NH(C1-C4 \text{ alkyl}), N(C1-C4 \text{ alkyl})_2, CN, CONH_2, CON(C1-C4 \text{ alkyl})_2, CO_2H, SO_2NH_2, SO_2NH(C1-C4 \text{ alkyl});$

$Y = \text{single bond}, NH, N(C1-C4 \text{ alkyl}), O, S;$

$A = \text{an acidic function};$

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R^b is hydrogen; cyano; or an acidic side-chain
of the structure $-A$ or $-(CH_2)_n-X-(CH_2)_m-Y-A$

where

$n = 0-4$

5 $m = 0-4$

$X = CHR^3$, $CH=CH$, phenylene ($-C_6H_4-$), NH , $N(C1-C4 \text{ alkyl})$, O , S , $S=O$, $C=O$,
 SO_2 , SO_2NH , CO_2 , $CONH$, OCO , $OC=O$, $NHC=O$;

$R^3 = H$, $O(C1-C4 \text{ alkyl})$, NH , $NH(C1-C4 \text{ alkyl})$, $N(C1-C4 \text{ alkyl})_2$, CN , $CONH$,
10 $CON(C1-C4 \text{ alkyl})_2$, CO_2H , SO_2NH_2 , $SO_2NH(C1-C4 \text{ alkyl})$;

$Y = \text{single bond}$, NH , $N(C1-C4 \text{ alkyl})$, O , S ;

$A = \text{an acidic function}$;

15 provided that R^a or R^b must be an acidic side-chain.

14. A compound of Claim 13 wherein the acidic
function $-A$ is a member selected from the group
consisting essentially of carboxy (CO_2H), phosphono [$P=O(OH)_2$],
20 alkylphosphono [$P=O(OH)(O(C1-C4 \text{ alkyl}))$], alkylphosphinyl [$P=O(OH)(C1-C4$
alkyl)], substituted phosphoramido [$P=O(OH)NH(C1-C4 \text{ alkyl})$] and
 $P=O(OH)NHR^x$], sulfinio (SO_2H), sulfo (SO_3H), 5-tetrazolyl (CN_4H),
arylsulfonamido (SO_2NHR^x) and acylsulfonamides represented by the structures
25 $CONHSO_2(C1-C4 \text{ alkyl})$, $CONHSO_2N(C1-C4 \text{ alkyl})$, $SO_2NHCO(C1-C4 \text{ alkyl})$ and
 SO_2NHCOR^x wherein $R^x = \text{aryl or heteroaryl}$.

15. A pharmaceutical composition for antibiotic
use comprising an antibacterially effective amount of
30 a compound of Claim 14, an inhibitorily effective amount
of a DHP inhibitor, and, optionally, a pharmaceutical
carrier.



European Patent
Office

EUROPEAN SEARCH REPORT

0167139

Application number

| DOCUMENTS CONSIDERED TO BE RELEVANT | | | EP 85108135.6 |
|---|---|--|---|
| Category | Citation of document with indication, where appropriate, of relevant passages | Relevant to claim | CLASSIFICATION OF THE APPLICATION (Int. Cl. 4) |
| X | DE - A1 - 3 334 937 (BRISTOL-MYERS CO.) * Claims 1,2,4,6-8,10,12,17,167 * | 1-8, 13,14 | C 07 D 487/04 A 61 K 31/40 C 07 D 519/00 |
| Y | * Claim 167 * | 9-12, 15 | |
| | -- | | |
| D, YEP | - A1 - 0 007 614 (MERCK & CO. INC.) * Claims 1,7; page 17, lines 5,6 * | 9-12, 15 | |
| | -- | | |
| D, YEP | - A1 - 0 072 014 (MERCK & CO. INC.) * Claims 1,7,14 * | 9-12, 15 | |
| | -- | | |
| A | EP - A1 - 0 021 082 (MERCK & CO. INC.) * Claims 1,3,5 * | 1-8, 11,13-15 | TECHNICAL FIELDS SEARCHED (Int. Cl. 4) C 07 D 487/00 A 61 K 31/00 C 07 D 519/00 |
| | ----- | | |
| The present search report has been drawn up for all claims | | | |
| Place of search VIENNA | | Date of completion of the search 25-09-1985 | Examiner PETROUSEK |
| CATEGORY OF CITED DOCUMENTS | | | |
| X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document | | T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons A : member of the same patent family, corresponding document | |

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